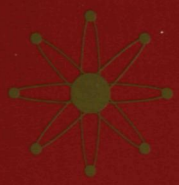


Radioiodine treatment of nodular goiter

Dyde Huysmans

Radioiodine treatment of nodular goiter

CIP-DATA KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Huysmans, Dymphna Ardina Katrien Charles Joseph Maria

Radioiodine treatment of nodular goiter / Dymphna Ardina Katrien Charles Joseph Maria Huysmans ; [ill.: Ch. Huysmans]. - [S.l. : s.n.]. - Ill.
Thesis Nijmegen. - With ref.
ISBN 90-9007997-1
Subject headings: radioactive iodine / nodular goiter

This thesis was set in New Century Schoolbook,
using the TEX typesetting system.
Design & layout: M.N.I.F.J.M. Huysmans.
Printing: Drukkerij SSN, Nijmegen

The printing of this thesis was financially supported by
Organon Nederland BV and Mallinkrodt Medical BV

Radioiodine treatment of nodular goiter

Een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

Proefschrift ter verkrijging van de graad van
doctor aan de Katholieke Universiteit Nijmegen,
volgens besluit van het College van Decanen
in het openbaar te verdedigen op donderdag
23 februari 1995 des namiddags te 3.30 uur precies

door

Dymphna Ardina Katrien Charles
Joseph Maria Huysmans
geboren op 26 april 1963 te Breda

Promotores:	Prof. Dr. F.H.M. Corstens
	Prof. Dr. P.W.C. Kloppenborg
Co-promotor:	Dr. A.R.M.M. Hermus

Afdelingen Nucleaire Geneeskunde en Endocriene Ziekten
Academisch Ziekenhuis St. Radboud, Nijmegen

Voor Pa en Ma, Heeroom, en Ad

Contents

Chapter 1 *1*
Introduction
1.1 Definitions
1.2 Pathogenesis of multinodular goiter
1.3 Natural history of multinodular goiter
1.4 Pathogenesis of solitary autonomous thyroid nodules
1.5 Natural history of solitary autonomous thyroid nodules
1.6 Effects of radioiodine treatment on the thyroid gland
1.7 Outline of the present thesis

Chapter 2 *23*
Thallium-201 scintigraphy of the suppressed thyroid:
an alternative for iodine-123 scanning after TSH stimulation
Journal of Nuclear Medicine 1988;29:1360–3

Chapter 3 *33*
Long-term follow-up in toxic solitary autonomous thyroid nodules
treated with radioactive iodine
Journal of Nuclear Medicine 1991;32:27–30

Chapter 4 *43*
Long-term results of two schedules of radioiodine treatment
for toxic multinodular goiter
European Journal of Nuclear Medicine 1993;20:1056–62

Chapter 5 *59*
Significance of TSH levels below the normal range
in patients treated with radioiodine for toxic multinodular goiter

Chapter 6 *69*
Magnetic resonance imaging for volume estimation of
large, multinodular goiters: a comparison with scintigraphy
British Journal of Radiology 1994;67:519–23

Chapter 7 *81*
Large, compressive goiters treated with radioiodine
Annals of Internal Medicine 1994;121:757–62

Chapter 8 *97*
Dosimetry and risk estimates of radioiodine therapy
of large, multinodular goiters
Submitted for publication

Summary *117*

Samenvatting *123*

Dankwoord *131*

Curriculum Vitæ *132*

Chapter

one

Introduction

In this thesis the effects of radioiodine treatment in patients with toxic and non-toxic multinodular goiter and in patients with toxic autonomous thyroid nodules are studied. This first chapter contains a short review of current knowledge of the pathogenesis and natural history of both entities and a summary of the cell biological effects of radioiodine on the thyroid gland.

In this thesis the effects of radioiodine treatment in patients with toxic and non-toxic multinodular goiter and in patients with toxic autonomous thyroid nodules are studied. This first chapter contains a short review of current knowledge of the pathogenesis and natural history of both entities and a summary of the cell biological effects of radioiodine on the thyroid gland.

1.1 Definitions

Goiter may be defined as any enlargement of the thyroid gland [1]. It is called endemic when the prevalence in a population is more than 10%. Endemic goiter is usually associated with iodine deficiency. The term sporadic goiter is used when goiter prevalence in a population is 10% or less [2].

Multinodular goiter is defined as a structurally and functionally heterogeneous thyroid enlargement [3]. According to Studer [4–6], multinodular goiter arises from excessive replication of thyroid epithelial cells with subsequent generation of new follicles of widely differing structure and function. The size of such a goiter tends to increase with age and, although the thyroid may be diffusely enlarged in the first phase of goitrogenesis, it will become more nodular with time. Moreover, euthyroidism may gradually change into hyperthyroidism in these patients.

A solitary autonomous thyroid nodule is a discrete thyroid nodule that secretes thyroid hormone independently of any known extrathyroidal stimulus [7]. It may exist in close approximation to and within normal thyroid parenchyma that remains subject to the functional regulation of the pituitary. As a solitary autonomous thyroid nodule is generated from follicular cells with, probably genetically determined, high replication rate and iodinating capacity, its size tends to increase with time, not infrequently leading to hyperthyroidism.

1.2 Pathogenesis of multinodular goiter

Increased cell replication as basis for goitrogenesis

Studer's group in Bern clearly demonstrated that nodular goiter is caused by excessive replication of thyroid epithelial cells with subsequent generation of new follicles. For example, Ramelli *et al.* [8] showed a highly significant, linear correlation between the total DNA content of multinodular goiters and the

weight of these goiters indicating that new cells must be generated during goiter growth. Histologically, these cells appeared to be mainly thyroid follicular epithelial cells.

The process of excessive cell replication and formation of new follicles is, however, not exclusive for multinodular goiters. It is also the basis for the formation of diffuse goiters in patients with Graves' disease. It seems that after a strong growth stimulation as in Graves' disease thyroid growth will be diffuse and follicle formation will be uniform because replication and metabolic function of all follicular cells are stimulated. In contrast, chronic, and possibly intermittent, mild stimulation gives rise to the very heterogeneous growth of nodular goiters [4].

Factors which may be involved in increased cell replication (growth stimulating factors)

Goitrogenesis can be stimulated by a number of factors. Thyroid-stimulating hormone (TSH) is the most potent thyroid growth stimulating factor *in vivo* [9, 10]. Thyroid growth due to iodine deficiency, exposure to goitrogens or the presence of inherited metabolic defects within the thyroid follicular cell is probably mediated by an increase of serum TSH levels, caused by a decrease of serum thyroid hormone levels.

Iodine deficiency is world-wide the most common cause of goiter. Iodine kinetics during iodine deficiency have been studied extensively in humans [11–18] and in animals [19–21]. A decrease in the intrathyroidal iodine pool leads to decreased iodination of thyroglobulin [14, 15, 17–19, 22] and diminished release of iodinated thyroid hormones. This subsequently causes a small increase in the serum TSH level, which results in a rise of iodine uptake and organification, thyroid hormone secretion and in thyroid growth. Although goitrogenesis in iodine deficiency is largely dependent on TSH stimulation, there is evidence that part of the process is TSH-independent [19]. In iodine deficient individuals thyroid growth is enhanced by ingestion of antithyroid substances, naturally occurring in certain plants (thiocyanates and thioglucosides). It is uncertain whether these agents are ever ingested in large enough quantities to cause goiter in the absence of iodine deficiency. Thyrostatic agents and some other drugs (*e.g.*, aminoglutethimide, phenylbutazone, ethionamide, iodine-containing agents, lithium, resorcinol, para-aminosalicylic acid) also occasionally cause goiter [3]. Various metabolic disorders at the level of the follicular cell, most of which are partial enzymatic defects, may cause familial goitrogenesis [23].

More recently, experimental evidence has been presented that growth factors like epidermal growth factor and insulin-like growth factor-1 and -2 may

be important for stimulation of goitrogenesis, partly via TSH-independent pathways [24–27]. Furthermore, the presence of thyroid growth stimulating immunoglobulins has been reported in serum of patients with non-toxic goiter [28]. Various reports favouring the existence of such thyroid growth stimulating immunoglobulins, using different methods for the assessment of growth, have been published [29–34]. Other studies could not confirm a pathogenetic role of thyroid growth stimulating immunoglobulins in nodular goiter [35–38]. There are many pitfalls in the methods used for growth assessment and purification of immunoglobulins [39]. Zakarija and McKenzie [40] concluded, therefore, that the existence and possible growth-promoting role of thyroid growth stimulating immunoglobulins in nodular goiter are still to be proved.

In addition to and possibly modulated by these extracellular stimulators of thyroid growth, some intracellular mechanisms have been proposed as possibly contributing to the growth of multinodular goiters. Studer *et al.* [41] reported on the presence in nodular goiters of clusters of thyroid follicular cells, heavily loaded with the protein product of the ras protooncogene. This protein participates in the transduction of growth-promoting signals and increased expression of the ras protooncogene is associated with increased cell replication [42, 43]. Recently, high intracellular levels of stimulatory guanine nucleotide binding (Gs) proteins in a fraction of cells of growing nodular goiters have been reported [44]. Gs proteins may stimulate growth by activation of the cyclic AMP cascade. Resistance of subpopulations of thyroid follicular cells to the antiproliferative effect of transforming growth factor β_1 may be another mechanism in goitrogenesis [45].

Heterogeneity between and within follicles and nodules in multinodular goiters

The heterogeneity of nodular goiter follicles is based on the fact that, even in individual follicles, thyroid cells may originate from different mother cells [46–48]. The polyclonal origin of epithelial cells in normal human thyroid tissue and in nodular goiter tissue has recently been confirmed by the X inactivation approach [49, 50]. Individual traits are transferred from a mother cell to all daughter cells [9, 51]. Especially those cells in a follicle, that have an inherited propensity to replicate at a higher rate than other cells, give rise to the generation of new follicles. In the course of goitrogenesis, therefore, the heterogeneity between follicles is amplified. Furthermore, during every replication cycle new metabolic traits, not present in the mother cell, can be acquired. Various mechanisms for the extragenetic acquirement of new cell qualities have been proposed [52–56]. These acquired traits may be transferred to subsequent generations of cells.

Experimental evidence of differences in replicating activity between thyroid cells in the normal thyroid gland as well as in multinodular goiters
Studer's group demonstrated differences in the replicating activity of individual cells of the rat thyroid cell line FRTL-5. This individual multiplication rate was reproducible in daughter cells, even after separation from the mother cell [5]. The same group also studied the replicating activity of thyroid cells by autoradiography showing the incorporation of a [^{3}H]thymidine label in cell nuclei during mitosis [9, 51, 58, 59]. Experiments in L-thyroxine (T_4) treated mice [58] demonstrated that in mouse thyroid glands the number of autonomously (*i.e.* in the absence of TSH stimulation) proliferating cells gradually declines with increasing age. [^{3}H]thymidine labelling was also used in experiments in human thyroid tissue (fetal and normal adult thyroid tissue and nodular goiter tissue) transplanted onto T_4 treated nude mice. Considerable autonomous proliferation of human fetal thyroid tissue was demonstrated [58]. Up to 36% of the fetal follicular cell nuclei incorporated the [^{3}H]thymidine label in the absence of TSH in the blood. For normal adult thyroid tissue the fraction of autonomously replicating cells was less than 1% and for human nodular goiter it ranged from 0.5% to 7% [9]. The authors hypothesized that the cells with high growth potential in the fetal thyroid gland are the same cells that replicate at a higher than average rate in the adult gland. During maturation, fetal cells acquire mechanisms that make them gradually less autonomous and more dependent on growth factors (like TSH). However, a few cells may fail to do so. The fraction of these growth prone cells in the individual adult gland may be important for the chance of developing nodular goiter.

Using autoradiography it was shown that in mouse thyroids, after growth stimulation by hemithyroidectomy, the majority of [^{3}H]thymidine labelled cells were clustered in groups of three or more, rather than being randomly distributed [59]. For human nodular goiter tissue grafted onto nude mice a large interregional variability of growth was observed with very dense clustering of [^{3}H]thymidine labelled cells in a few distinct regions. Individual follicles contained variable numbers of labelled cell clusters consisting of only a few cells to a multitude of replicating cells [9, 51]. The newly formed cells closely stayed together to form large families. Therefore, it appeared that the growth advantage of these cells is conveyed from mother to daughter cells. The replicating potential of individual cells was not correlated with any specific cell morphology.

TSH stimulation by feeding the nude mice methimazole resulted in an increase of the fraction of [^{3}H]thymidine labelled cells in both normal and goitrous human thyroid tissue. A TSH-dependent recruitment of follicular cells was found [9]: upon a small increase in TSH levels a further set of cells, not autonomously replicating but with a low threshold for TSH response, starts to

proliferate and with increasing intensity and duration of the stimulus the percentage of replicating cells expands gradually.

Experimental evidence for differences in metabolic functions between thyroid cells in the normal thyroid gland as well as in multinodular goiters

Intercellular diversity of various metabolic functions has been demonstrated within and between follicles and nodules in multinodular goiters. *In vitro*, considerable intercellular differences in activities of enzymes needed for thyroid metabolism [peroxidase, deiodinase, thyroglobulin acid hydrolases and adenylcyclase] have been reported [51, 60–63]. Furthermore, *in vitro* intercellular differences in thyroglobulin synthesis have been shown using plaque-forming assays with single thyrocytes [64] and the in situ hybridization technique [65].

In vivo, different aspects of metabolic heterogeneity have been evaluated. A variable degree of autonomous, *i.e.* TSH-independent, iodide uptake in normal follicles was found in hypophysectomized animals [20] and in the extranodular thyroid tissue of patients with a toxic solitary autonomous nodule [66–68]. Diversity of iodination of intraluminal iodoproteins was also demonstrated by autoradiography after ^{131}I or ^{125}I labelling of mouse thyroids [4, 69], surgical specimens of feline goiters [70] and of human goiters [51] and feline and human goiters transplanted onto nude mice [9, 70]. The degree of autonomous iodide organification during TSH suppression differs between cells or cell groups within a single follicle [9, 51]. Moderate TSH stimulation increases ^{125}I uptake in both hot and cold follicles. Heavy stimulation, like in Graves' disease, will gradually level off the heterogeneity in iodine metabolism, because an upper limit to the iodine turnover is reached.

Endocytosis of colloid is characterized by pseudopods protruding into the follicular lumen followed by the appearance of thyroglobulin-filled droplets within follicular cells [51]. In the absence of TSH the number of droplet-containing cells and the droplet count per cell, as studied in rat and mouse thyroids, are very low. With increasing TSH concentrations, the number of droplet-containing cells as well as the number of droplets per cell gradually increase up to a plateau [21]. Increasing endocytosis with rising TSH concentrations was also reported using electron microscopical quantification of pseudopod number and size [71]. An age dependent failure of TSH-responsive endocytosis has been observed in an increasing number of follicles of aging mice [72]. Subsequent overfilling of the follicular lumina with colloid leads to a cease of iodine uptake and irreversibly "cold" follicles.

The colloid content of a follicle depends on the total thyroglobulin synthesis of the individual follicle cells and on their endocytotic activity. In human goiters

diversity of thyroglobulin synthesis and endocytosis is apparent from marked differences in size and thyroglobulin content of follicles. In the normal thyroid, every follicular cell contributes a rather constant share to the total luminal store of colloid, resulting in a constant thyroglobulin content of about 4% of the dry weight of a thyroid tissue sample. In contrast, thyroglobulin content in nodular goiters differs widely between regions [4].

Consequences of increased cell replication and cellular heterogeneity

During goiter growth the fraction of cells with a high growth rate expands at the expense of slower growing cells. Due to this growing fraction of rapidly replicating cells the growth rate of the whole goiter increases. New follicular cells may form new follicles or they may be used to enlarge the envelope of the mother follicle [41]. Large colloid rich follicles and microfollicular regions may coexist in the same goiter. The newly formed thyroid tissue requires expansion of the capillary network which is often grossly different from normal vessels [4]. The abnormal capillaries may fail to adequately supply the newly formed thyroid cells. Scattered haemorrhagic necroses with collaps and destruction of follicles and with interspersed strands of connective tissue are characteristic results of this process [73]. Necrotic areas are invaded by granulation tissue and ultimately poorly cellular scars may form, creating a fibrous network interfering with smooth growth which will further enhance (pseudo-)nodularity.

In nodular goiter the fine balance between cell functions which prevails in normal glands is lost [74]. Any metabolic function may be autonomous. Small follicles with suppressible iodide uptake result when only replication and endocytosis are autonomous. When iodide uptake is also autonomous, small follicles with non-suppressible iodide uptake result. When thyroglobulin synthesis and iodine organification but not endocytosis are autonomous, large colloid rich follicles will form with non-suppressible iodide uptake [73]. Thus, metabolic function cannot be deduced from the microscopical appearance of follicles or individual cells [9, 51, 72, 75, 76].

Autonomous iodine turnover in thyroid follicles is essentially a physiological phenomenon. However, when the number of follicles with autonomous iodine turnover increases in a nodular goiter, the total amount of thyroid hormones secreted by these and by TSH-dependent follicles may exceed the amount needed by the organism. TSH levels will become suppressed (autonomous thyroid function) and ultimately overt hyperthyroidism will develop [77, 78].

1.3 Natural history of multinodular goiter

The aforementioned cell biological data suggest that the natural history of (nodular) goiter is characterized by growth, increasing nodularity and increasing autonomy of thyroid metabolic functions. Berghout *et al.* [37, 79] indeed found evidence for continuous growth and increasing nodularity in non-toxic goiter. In a cross-sectional study of 102 consecutive patients with sporadic non-toxic goiter [79] they showed that patients with a multinodular goiter were older and had a larger thyroid volume than patients with a diffuse or uninodular goiter (ultrasonography measurements). Thyroid volume was positively correlated with age and duration of goiter. They calculated an annual increase of thyroid volume of 4.5%. In a longitudinal placebo-controlled study on the effects of L-thyroxine on thyroid volume in patients with non-toxic goiter the same group observed a steady increase in thyroid volume in the 26 subjects who were treated with placebo [37]. In this group the mean increase of thyroid volume at 18 months was 27%, probably reflecting a selection of patients with faster growing goiters for participation in this trial.

Thyroid function in nodular goiter was studied cross-sectionally by several authors. Miller *et al.* [66] reported the presence of functional autonomy, as assessed by insufficient suppression of thyroid radioactive iodide uptake after exogenous triiodothyronine administration, in 66% of patients with euthyroid multinodular goiter, especially in elderly patients. Gemsenjäger *et al.* [80] and Emrich *et al.* [81] observed thyroid functional autonomy, defined as an absent or subnormal TSH rise after injection of thyrotropin releasing hormone (TRH), in a lower percentage (approximately 20%) of patients with non-toxic goiter in endemic as well as in sporadic areas. The cross-sectional study by Berghout *et al.* [79] showed that plasma free T_4 levels and total T_3 levels were higher and TSH levels were lower in patients with non-toxic goiter compared with normal subjects. The subgroup with multinodular goiter had a significantly lower TSH response to an injection of TRH in comparison with that in the subgroups with diffuse or uninodular goiter. Plasma TSH was negatively correlated with thyroid volume. An increase in the frequency of thyroid functional autonomy with age, duration of goiter, goiter weight and nodularity was also observed by other authors in cross-sectional studies [80–83].

Cross-sectional data in support of increasing functional autonomy of nodular goiter with time were confirmed in longitudinal studies. Elte *et al.* [84] followed 90 patients with a nodular goiter for a mean duration of 5 years. At the time of diagnosis, 64 patients had autonomous thyroid function, defined as a TSH increase after TRH injection of less than 4 mU/l in combination with normal

T_3 and free T_4 levels. Six patients showed a transition from normal to autonomous function, and eight patients with autonomous function became overtly hyperthyroid within 1 to 7 years. In one patient the complete transition from nonautonomous function via functional autonomy to hyperthyroidism was observed. Wiener [85] reported on the follow-up (5 to 22 years) of 28 patients with euthyroid multinodular goiter. Four of 28 patients developed hyperthyroidism during follow-up, thus confirming increasing functional autonomy.

1.4 Pathogenesis of solitary autonomous thyroid nodules

Solitary autonomous thyroid nodules can be classified as either true adenomas or adenomatous nodules [86]. True thyroid adenomas are benign, cellular tumors consisting of follicular cells with an abnormal but uniform architectural pattern. They have a well-defined fibrous capsule. Adenomatous nodules are solitary lesions which typically contain areas of normal follicular architecture but have no capsule. True adenomas have a monoclonal origin, while adenomatous nodules are polyclonal [87]. In countries where the overall goiter incidence is low, solitary autonomous thyroid nodules are more often of the clonal, encapsulated type than in (sub-)endemic areas [73, 88].

Although it has been suggested that solitary autonomous thyroid nodules may be caused by thyroid-stimulating immunoglobulins [30, 32], these nodules are more probably caused by an intrathyroidal defect and not by a circulating factor: they coexist with normal (suppressed) thyroid tissue and hyperactivity persists in solitary autonomous thyroid nodules grafted onto nude mice [89] and in cell culture [90]. Solitary autonomous thyroid nodules are likely to be generated from follicular cells with genetically determined high replication rate and iodinating capacity [91, 92]. Indeed, somatic mutations of the Gs_α gene [93] as well as somatic mutations of the TSH receptor gene have been reported in a number of solitary autonomous thyroid nodules [94, 95]. Hyperthyroidism develops when the number of follicles with non-suppressible thyroid hormone production is large enough to produce more thyroid hormone than is needed by the organism. In this way solitary autonomous thyroid nodules can be considered an extreme and localized type of nodular growth and autonomous function.

1.5 Natural history of solitary autonomous thyroid nodules

The incidence of solitary autonomous thyroid nodules appears to be higher in Europe (9% of thyrotoxic patients in a prospective study in six European countries) [96] than in the United States (only 1% of patients referred to a thyroid clinic) [97]. This higher incidence is possibly related to former or current iodine deficiency in European countries [96, 98].

Solitary autonomous thyroid nodules tend to increase with age. Cross-sectional studies [99, 100] showed a positive correlation between age and nodule size. Longitudinal studies demonstrate similar results. Hamburger *et al.* [97] observed an increase in diameter of solitary autonomous thyroid nodules of more than 1 cm in 9% of 159 patients after a follow-up up to 15 years.

The function of the autonomous nodule is inversely related to that of the extranodular tissue. Non-toxic autonomous nodules are much more common than toxic ones [97, 99, 101, 102]. The presence of hyperthyroidism correlates with age and nodule size [99, 100, 103–106]. Progression to hyperthyroidism in patients with non-toxic solitary autonomous thyroid nodules occurred in 14 of 159 patients during a follow-up of 1 to 6 years in a study by Hamburger *et al.* [97]. The same group reported development of hyperthyroidism in 21% of 127 patients with a non-toxic solitary autonomous thyroid nodule during a follow-up up to 6 years and in 14% of patients who were followed for 7 to 15 years [106]. In a study by Wiener [85], 17% of 46 patients became hyperthyroid during a follow-up of 5 to 22 years. Belfiore *et al.* [98] reported development of hyperthyroidism in 4 of 14 patients (29%) with a non-toxic solitary autonomous nodule in an iodine deficient area and in 11 of 58 patients (19%) in an iodine sufficient area during a follow-up of 1 to 6 years. In contrast, Burman *et al.* [101] observed no development of hyperthyroidism in 46 patients with a non-toxic solitary autonomous thyroid nodule after a follow-up of more than 6 years.

Degeneration of the nodule may preclude the development of hyperthyroidism [7, 85, 101, 107]. The highly cellular nodules are prone to central haemorrhage and subsequent cyst formation because they contain only few, thin walled vessels almost without any connective tissue support. On scintigraphy this phenomenon is known as the "owl eye" sign, a cold centre surrounded by a rim of high iodine uptake [107] which should not be confused with a true cold nodule.

1.6 Effects of radioiodine treatment on the thyroid gland

The first reports on treatment of hyperthyroidism with radioactive iodine, administered as sodium iodide, date from 1942 [108, 109]. Since cyclotron produced iodine-131 (^{131}I) was released for distribution within the United States by the National Energy Commission in 1946, its use in diagnostic tests and therapy has rapidly increased. ^{131}I desintegrates to Xenon-131 with a physical half-life of 8.04 days [110]. During desintegration of ^{131}I beta particles (electrons) are emitted, which in 90% of desintegrations have an average energy of 190 keV. Furthermore, gamma particles (photons) are emitted. In 80% of transitions these photons have an energy of 364 keV (energies range between 30 and 723 keV). Radiation energy is transferred to atoms during collisions of the radiation particles with atomic electrons in substances, *e.g.*, human tissues. Beta particles transfer kinetic energy to atoms by ionization (an electron is emitted from the atom) and excitation (an electron is removed from an inner shell to an outer shell of the atom). Gamma particles are scattered (Compton scatter) or absorbed (photo-electric effect) within tissues and lose part or all of their energy during these processes, thereby also inducing ionization and excitation of atoms.

On the molecular level, the primary event in the initiation of biological damage is the radiolysis of water (H_2O), the most abundant molecule in all biological systems. Within a fraction of a second hydroxyl and hydrogen free radicals ($OH^\bullet$ and $H^\bullet$) are formed, which contain unpaired electrons [111, 112]. Free radicals may undergo many reactions. Two $OH^\bullet$ free radicals may combine to form hydrogen peroxide (H_2O_2), a powerful oxidizing agent. Reactions of free radicals with other components of the cell lead to the production of excited ions and molecules and other types of free radicals. Reactions of free radicals with proteins cause changes in the secondary or tertiary structure of proteins by disruption of hydrogen bounds which produce severe alterations of the biological properties of these molecules such as complete loss of enzymatic activity. Other important reactions occur with the deoxyribonucleic acids (DNA) of the cell nucleus. The breakage or cross-linking of DNA molecules may have particularly serious effects, ranging from loss of the cell's capacity to divide to the production of mutations [112]. Three types of cellular changes, caused by these chemical changes of proteins and DNA, are recognized, namely early cell death, prevention or delay of cell division and permanent, inheritable changes which may be passed on to daughter cells. Cellular changes may lead to other changes which affect the whole organism, showing a most variable time scale from a few hours to many years.

In the case of radioiodine, an administered activity of ^{131}I follows the natural biokinetic pathway of iodine. The high specific activity of ^{131}I (111–185 megabecquerel per microgram (MBq/μg) or 3–5 millicurie per microgram (mCi/μg)) allows that the total amount of iodine is negligibly low in comparison to the daily intake of iodine. Part of the administered dose, corresponding to thyroid iodide uptake, is deposited in the thyroid, organified and stored in the colloid of thyroid follicles. Beta particles emitted by ^{131}I in the thyroid will irradiate almost exclusively thyroid cells and their immediate environment because they transfer their kinetic energy within a maximal distance of 3 mm, whereas their average range in tissues is even smaller, only 0.3 mm. Gamma particles emitted by ^{131}I in the thyroid gland are less important for the therapeutic irradiation of the thyroid, because their energy is transferred over a much longer distance (photons have less interaction with tissue atoms because they have no charge or mass). However, gamma radiation does contribute considerably to the irradiation burden of the rest of the body.

Therapeutic activities of ^{131}I cause radiation-induced destruction of thyroid parenchyma. Within the first few weeks after treatment, epithelial swelling and necrosis occur, accompanied by disruption of the follicular architecture, edema and infiltration with leucocytes [113, 114]. This radiation thyroiditis may cause local tenderness and in rare cases thyrotoxicosis due to excessive thyroid hormone release. Resolution of the acute inflammation is followed by fibrosis, vascular narrowing and lymphocytic infiltration [113, 115]. These structural changes are responsible for the early response to radioiodine treatment and, when excessive, they cause early hypothyroidism.

Apart from early effects of radioiodine, late effects on thyroid function have been recognized, especially in patients with Graves' disease. There is an increasing incidence of hypothyroidism in these patients, even several years after therapy. The rate of early hypothyroidism in radioiodine treated Graves' patients is dose related. However, late hypothyroidism (*i.e.* occurring more than two years after radioiodine therapy) appears to be dose-independent. Various mechanisms may contribute to the development of late hypothyroidism, such as damage to follicular cell nuclei, resulting in failure to replicate, reaching of an upper limit of the proliferative capacity of the population of mitotically competent cells, progressive impairment of blood supply and the natural history of Graves' disease [116].

The incidence of early as well as of late hypothyroidism after treatment with radioiodine is probably much lower in patients with toxic nodular goiter than in patients with Graves' disease. This may be related to the diversity in radioiodine uptake between nodular goiter follicles. Autonomously functioning

thyroid follicles with high uptake of radioiodine will be eradicated preferentially, whereas radioiodine uptake in normal, TSH-dependent follicles is low in the presence of suppressed TSH levels. Furthermore, cells with a high replication rate are destroyed more effectively. These mechanisms can be observed most clearly in the treatment of solitary autonomous thyroid nodules (chapter three of this thesis).

Other possible late consequences of radioiodine therapy are radiation-induced carcinogenic and teratogenic effects due to mutations of the DNA. This will be discussed in more detail in chapter eight of this thesis. Suffice it now to mention that no carcinogenic or teratogenic effects of radioiodine in the dosages administered in Graves' disease have been observed in large series with follow-up up to 35 years [117–119].

1.7 Outline of the present thesis

Results of radioiodine therapy have been evaluated extensively in patients with Graves' disease. Considerably less reports have been published on radioiodine treatment in patients with nodular goiter. In this thesis, attention is paid to various aspects of radioiodine treatment of patients with toxic and non-toxic multinodular goiter and of patients with toxic solitary autonomous thyroid nodules. Seven studies are presented (chapters two to eight).

Chapter two
The value of thallium-201 scintigraphy to visualize extranodular thyroid tissue in patients with a toxic solitary autonomous thyroid nodule was studied prospectively and compared with results obtained by ^{123}I scintigraphy after TSH stimulation. Demonstration of suppressed extranodular tissue in these patients is important, because when it is present higher amounts of radioiodine can be administered without causing hypothyroidism.

Chapter three
In our hospital a standard dose of 20 mCi (740 MBq) of ^{131}I is administered to treat patients with a toxic solitary autonomous thyroid nodule. In this study we evaluated the long-term results of this treatment schedule.

Chapter four
A study on the long-term effects of two schedules of radioiodine treatment in patients with toxic multinodular goiter. Low, standard doses of radioiodine and higher, calculated doses are compared with regard to the time to reach euthyroidism and the incidence of post-therapy hypothyroidism.

Chapter five
In the study described in chapter four 30% of euthyroid patients had a subnormal serum TSH level at the time of the last evaluation. As the significance of the combination of a normal fT_4 and T_3 level with a subnormal TSH level in a patient treated with radioiodine with respect to the risk of recurrent hyperthyroidism is unknown, we followed thyroid function for another year in the whole group of euthyroid patients and for another two years in a subgroup of patients, who had been rendered euthyroid after a single calculated dose of radioiodine.

Chapter six
Thyroid volume measurements by palpation or scintigraphy are known to be inaccurate. Ultrasound is a more precise technique, but it cannot be used for volume measurements of large multinodular goiters because of intrathoracic extension of the goiter in most patients. In patients with a large multinodular goiter we compared thyroid volume measurements with magnetic resonance imaging (MRI) with those obtained with the commonly used planar scintigraphic technique.

Chapter seven
A prospective study is described on thyroid volume reduction by radioiodine therapy in patients with a large, compressive multinodular goiter. In this study MRI was used for accurate evaluation of thyroid volume reduction and decrease of tracheal compression.

Chapter eight
For volume reduction of large multinodular goiters high doses of radioiodine are needed. We gathered data on radiation absorbed doses after radioiodine treatment in patients with large toxic and non-toxic multinodular goiters, in order to get an impression of the radiation burden.

1.8 References

1 Perez C, Scrimshaw NS, Munoz JA. Technique of endemic goitre surveys. *In: Endemic Goitre; WHO Monograph Series* 1960;44:369–83

2 Studer H, Gebel F. Sporadic goiter. *In: Ingbar SH, Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid, 5th ed. Philadelphia: Lippincott* 1986:1311–15

3 Larsen PR, Ingbar SH. The thyroid gland. *In: Wilson JD, Foster DW, eds. Williams Textbook of Endocrinology, 8th ed. Philadelphia: Saunders* 1992:357–488

4 Studer H, Ramelli F. Simple goiter and its variants: euthyroid and hyperthyroid multinodular goiters. *Endocr Rev* 1982;3:40–61

5 Studer H. A fresh look at an old thyroid disease: euthyroid and hyperthyroid nodular goiter. *J Endocrinol Invest* 1982;5:57–68

6 Studer H, Gerber H. Pathogenesis of nontoxic diffuse and nodular goiter. *In: Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid, 6th ed. Philadelphia: Lippincott* 1991:1107–13

7 Hamburger JI. The autonomously functioning thyroid nodule: Goetsch's disease. *Endocr Rev* 1987;8:439–47

8 Ramelli F, Bürgi U, Siebenhüner L, Kohler H, Studer H. A disproportionate accumulation of fibrous tissue is not a causal factor in human goitre growth. *Acta Endocrinol (Copenh)* 1987;116:502–6

9 Peter HJ, Gerber H, Studer H, Smeds S. Pathogenesis of heterogeneity in human multinodular goiter. A study on growth and function of thyroid tissue transplanted onto nude mice. *J Clin Invest* 1985;76:1992–2002

10 Smeds S, Peter HJ, Gerber H, Jörtsö E, Lennquist S, Studer H. Effects of thyroxine on cell proliferation in human multinodular goiter: a study on growth of thyroid tissue transplanted to nude mice. *World J Surg* 1988;12:241–5

11 Choufoer JC, Van Rhijn M, Kassenaar AAH, Querido A. Endemic goiter in Western Guinea: iodine metabolism in goitrous and nongoitrous subjects. *J Clin Endocr* 1963;23:1203–17

12 Choufoer JC, Van Rhijn M, Querido A. Endemic goiter in Western Guinea II Clinical picture, incidence and pathogenesis of endemic cretinism. *J Clin Endocr* 1965; 25:385–402

13 Ermans AM, Kinthaert J, Camus M. Defective intrathyroidal iodine metabolism in nontoxic goiter: inadequate iodination of thyroglobulin. *J Clin Endocr* 1968; 28:1307–16

14 Agerbaek H, Jensen SE. Quantitative studies of iodine metabolism in sporadic, non-toxic goitre. An evaluation of pathogenesis. *Acta Endocrinol (Copenh)* 1974; 76: 67–73

15 Agerbaek H. Non-toxic goitre. The role of iodine deficiency in goitre formation in a non-endemic area. *Acta Endocrinol (Copenh)* 1974;76: 74–82

16 Hennemann G. Non-toxic goitre. *Clin Endocrinol Metab* 1979;8:167–79

17 Beckers C. Nontoxic goiter. *In: De Visscher M, ed. The Thyroid Gland. New York: Raven* 1980:231–55

18 Eastman CJ, Phillips DIW. Endemic goitre and iodine deficiency disorders: ætiology, epidemiology and treatment. *In:. Baillière's Clinical Endocrinology and Metabolism. London: Baillière Tindall* 1988:719–35

19 Studer H, Greer MA. A study on the mechanisms involved in the production of iodine-deficiency goiter. *Acta Endocrinol (Copenh)* 1965;49:610–28

20 Van Middlesworth L. Thyroxine accumulation in thyroids of hypophysectomized rats. *Endocrinology* 1969;84:375–80

21 Gerber H, Peter HJ, Bachmeier C, Kaempf J, Studer H. Progressive recruitment of follicular cells with graded secretory responsiveness during stimulation of the thyroid gland by thyrotropin. *Endocrinology* 1987;120:91–6

22 Wahner HW, Gaitan E, Correa P. Studies of iodine metabolism in endemic nodular goiter. *J Clin Endocr* 1966;26:279–86

23 Stanbury JB. Inherited metabolic disorders of the thyroid system. *In: Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid, 6th ed. Philadelphia: Lippincott* 1991:934–41

24 Roger PP, Dumont JE. Factors controlling proliferation and differentiation of canine thyroid cells cultured in reduced serum conditions: effects of thyrotropin, cyclic AMP and growth factors. *Mol Cell Endocrinol* 1984;36:79–93

25 Humphries H, MacNeil S, Munro DS, Tomlinson S. Interaction of epidermal growth factor with receptors on human and porcine thyroid membranes. *J Endocrinol* 1984;102:57–61

26 Tramontano D, Cushing GW, Moses AC, Ingbar SH. Insulin-like growth factor-1 stimulates the growth of rat thyroid cells in culture and synergizes the stimulation of DNA synthesis induced by TSH and Graves'-IgG. *Endocrinology* 1986;119:940–2

27 Maciel RMB, Moses AC, Villone G, Tramontano D, Ingbar SH. Demonstration of the production and physiological role of insulin-like growth factor-2 in rat thyroid follicular cells in culture. *J Clin Invest* 1988;82:1546–53

28 Drexhage HA, Botazzo GF, Doniach D. Evidence for thyroid-growth-stimulating immunoglobulins in some goitrous thyroid diseases. *Lancet* 1980;ii:287–92

29 McMullan NM, Smyth PPA. In vitro generation of NADPH as an index of thyroid stimulating immunoglobulins (TGI) in goitrous disease. *Clin Endocrinol (Oxf)* 1984;20:269–80

30 Wiener JD, Van der Gaag RD. Autoimmunity and the pathogenesis of localized thyroid autonomy (Plummer's disease). *Clin Endocrinol (Oxf)* 1985;23:635–42

31 Van der Gaag RD, Drexhage HA, Wiersinga WM, Brown RS, Docter R, Bottazzo GF, Doniach D. Further studies on thyroid growth-stimulating immunoglobulins in euthyroid nonendemic goiter. *J Clin Endocrinol Metab* 1985;60:972–9

32 Smyth PPA, McMullan NM, Grubeck-Loebenstein B, O'Donovan DK. Thyroid growth-stimulating immunoglobulins in goitrous disease; relationship to thyroid-stimulating immunoglobulins. *Acta Endocrinol (Copenh)* 1986;111:321–30

33 Schatz H, Pschierer-Berg K, Nickel JA, Bär R, Müller F, Bretzel RG, Müller H, Stracke H. Assay for thyroid growth stimulating immunoglobulins: stimulation of [^{3}H]thymidine incorporation into isolated thyroid follicles by TSH, EGF, and immunoglobulins from goitrous patients in an iodine-deficient region. *Acta Endocrinol (Copenh)* 1986;112:523–30

34 Wilders-Truschnig MM, Drexhage HA, Leb HA, Eber O, Brezinschek HP, Dohr G, Lanzer G, Krejs GJ. Chromatographically purified immunoglobulin G of endemic and sporadic goiter patients stimulates FRTL5 cell growth in a mitotic arrest assay. *J Clin Endocrinol Metab* 1990;70:444–52

35 Valente WA, Vitti P, Rotella CM, Vaughan MM, Aloy SM, Grollman EF, Ambesi-Impiombato FS, Kohn LD. Antibodies that promote thyroid growth; A distinct population of thyroid-stimulating autoantibodies. *N Engl J Med* 1983;309:1028–34

36 Chiovato L, Hammond LJ, Hanafusa T, Pujol-Borrell R, Doniach D, Bottazzo GF. Detection of thyroid growth immunoglobulins (TGI) by [^{3}H]-thymidine incorporation in cultured rat thyroid follicles. *Clin Endocrinol* 1983;19:581–90

37 Berghout A, Wiersinga WM, Drexhage HA, Smits NJ, Touber JL. A double-blind randomized trial comparing placebo with L-thyroxine or L-thyroxine in combination with carbimazole in the treatment of sporadic nontoxic goitre. *Lancet* 1990; 336:193–7

38 Wilders-Truschnig MM, Warnkroß H, Leb G, Langsteger W, Eber O, Tiran A, Dobnig H, Passath A, Lanzer G, Drexhage HA. The effect of treatment with levothyroxine or

iodine on thyroid size and thyroid growth stimulating immunoglobulins in endemic goitre patients. *Clin Endocrinol (Oxf)* 1993;39:281–6

39 Dumont JE, Roger PP, Ludgate M. Assays for thyroid growth immunoglobulins and their clinical implications: methods, concepts and misconceptions. *Endocr Rev* 1987;8:448–52

40 Zakarija M, McKenzie JM. Do thyroid growth-promoting immunoglobulins exist? *J Clin Endocrinol Metab* 1990;70:308–10

41 Studer H, Gerber H, Zbaeren J, Peter HJ. Histomorphological and immunohistochemical evidence that human nodular goiters grow by episodic replication of multiple clusters of thyroid follicular cells. *J Clin Endocrinol Metab* 1992;75:1151–8

42 Chang EH, Furth ME, Scolnick EM, Lowy DR. Tumorigenic transformation of mammalian cells induced by a normal human gene homologous to the oncogene of Harvey murine sarcoma virus. *Nature* 1982;297:479–83

43 Regulating ras. *Lancet* 1990;336:1291-2

44 Derwahl M, Hamacher C, Zbären J, Schatz H. Detection of activated Gs proteins in nodular goiters and thyroid adenomas by antibodies raised against a recombinant Gs protein. *J Endocrinol Invest* 1993;16 (suppl 2):63

45 Asmis L, Kopp P, Kämpf J, Von Grünigen C, Studer H. Resistance of thyroid follicular cells to the antiproliferative effect of transforming growth factor β_1: a possible mechanism in goitrogenesis. *J Endocrinol Invest* 1993;16 (suppl 2):63

46 Feder N. Solitary cells and enzyme exchange in tetraparental mice. *Nature* 1976; 263:67–9

47 Thomas GA, Williams D, Williams ED. The demonstration of tissue clonality by X-linked enzyme histochemistry. *J Pathol* 1988;155:101–8

48 Thomas GA, Williams ED. Aetiology of simple goitre. *In: Baillière's Clinical Endocrinology and Metabolism. London: Baillière Tindall* 1988:703–18

49 Fey MF, Peter HJ, Hinds HL, Zimmermann A, Liechti-Gallati S, Gerber H, Studer H, Tobler A. Clonal analysis of human tumors with M27β, a highly informative polymorphic X chromosomal probe. *J Clin Invest* 1992;89:1438–44

50 Kopp P, Kimura AT, Aeschimann S, Oestreicher M, Tobler A, Fey MF, Studer H. Polyclonal and monoclonal thyroid nodules coexist within human multinodular goiters. *J Clin Endocrinol Metab* 1994;79:134–9

51 Peter HJ, Studer H, Forster R, Gerber H. The pathogenesis of "hot" and "cold" follicles in multinodular goiters. *J Clin Endocrinol Metab* 1982;55:941–6

52 Adams JM. The organization and expression of immunoglobulin genes. *Immunol Today* 1980;1:10–7

53 Ziff EB. Transcription and RNA processing by the DNA tumour viruses. *Nature* 1980;287:491–9

54 Razin A, Cedar H. DNA methylation in eukaryotic cells. *Int Rev Cytol* 1984; 92:159–85

55 Slutsky B, Buffo J, Soll DR. High-frequency switching of colony morphology in Candida albicans. *Science* 1985;230:666–9

56 Gehring WJ. The homeo box: a key to the understanding of development? *Cell* 1985;40:3–5

57 Huber G, Derwahl M, Kaempf J, Peter HJ, Gerber H, Studer H. Generation of intercellular heterogeneity of growth and function in cloned rat thyroid cells (FRTL-5). *Endocrinology* 1990;126:1639–45

58 Peter HJ, Studer H, Groscurth P. Autonomous growth, but not autonomous function, in embryonic human thyroids: a clue to understanding autonomous goiter growth? *J Clin Endocrinol Metab* 1988;66:968–73

59 Smeds S, Peter HJ, Jörtsö E, Gerber H, Studer H. Naturally occurring clones of cells with high intrinsic proliferation potential within the follicular epithelium of mouse thyroids. *Cancer Res* 1987;47:1646–51

60 Van den Hove-Vandenbroucke MF, Couvreur-Eppe M, De Visscher M. Defective thyroglobulin endocytosis and hydrolysis in thyroid cold nodules. *Eur J Clin Invest* 1975;5:229–34

61 Conti A, Kneubuehl F, Studer H, Kohler H, Bürgi H. Increased iodotyrosine deiodinase activity in human goiters and in rats treated with perchlorate. *In: Robbins J, Braverman LE, eds. Thyroid Research, Excerpta Medica, ICS 378. Amsterdam: American Elsevier* 1976:166–8

62 Conti A, Studer H, Kneubuehl F, Kohler H. Regulation of thyroidal deiodinase activity. *Endocrinology* 1978;102:321–9

63 Rentsch H, Studer H, Frauchiger B, Siebenhüner L. Topographical heterogeneity of basal and thyrotropin-stimulated adenosine 3',5'-monophosphate in human nodular goiter. *J Clin Endocrinol Metab* 1981;53:514–21

64 Fontana S, Tramontano D, Ambesi-Impiombato FS, Rossi G. Thyroglobulin production by rat thyroid cells in culture: a study at the level of single cells. *Endocrinology* 1982;110:1790–5

65 Bergé-Lefranc JL, Cartouzou G, Bignon C, Lissitzky S. Quantitative in situ hybridization of ^{3}H-labeled complementary deoxyribonucleic acid (cDNA) to the messenger ribonucleic acid of thyroglobulin in human thyroid tissues. *J Clin Endocrinol Metab* 1983;57:470–6

66 Miller JM, Block MA. Functional autonomy in multinodular goiter. *JAMA* 1970;214:535–9

67 Wöhler J, Heinze HG, Pickardt CR, Erhardt F, Scriba PC. Eine neue, risikolose Methode zur Diagnostik dekompensierter autonomer Adenome der Schilddrüse. *Dtsch Med Wochenschr* 1974;99:1240–2

68 Studer H, Hunziker HR, Ruchti C. Morphologic and functional substrate of thyrotoxicosis caused by nodular goiters. *Am J Med* 1978;65:227–34

69 Wollman SH, Wodinsky I. Localization of protein-bound ^{131}I in the thyroid gland of the mouse. *Endocrinology* 1955;56:9–20

70 Peter HJ, Gerber H, Studer H, Becker DV, Peterson ME. Autonomy of growth and of iodine metabolism in hyperthyroid feline goiters transplanted onto nude mice. *J Clin Invest* 1987;80:491–8

71 Nilsson M, Engström G, Ericson LE. Graded response in the individual thyroid follicle cell to increasing doses of TSH. *Mol Cell Endocrinol* 1986;44:165–9

72 Studer H, Forster R, Conti A, Kohler H, Haeberli A, Engler H. Transformation of normal follicles into thyrotropin-refractory "cold" follicles in the aging mouse thyroid gland. *Endocrinology* 1978;102:1576–86

73 Miloni E, Studer H. Functional and morphological particularities of the autonomous follicles in human goiters. *J Mol Med* 1980;4:7–20

74 Masini-Repiso AM, Cabanillas AM, Bonaterra M, Coleoni AH. Dissociation of thyrotropin-dependent enzyme activities, reduced iodide transport, and preserved iodide organification in nonfunctioning thyroid adenoma and multinodular goiter. *J Clin Endocrinol Metab* 1994;79:39–44

75 Miller JM, Horn RC, Block MA. The autonomous functioning thyroid nodule in the evolution of nodular goiter. *J Clin Endocr* 1967;27:1264–74

76 Teuscher J, Peter HJ, Gerber H, Berchtold R, Studer H. Pathogenesis of nodular goiter and its implications for surgical management. *Surgery* 1988;103:87–93

77 Studer H, Peter HJ, Gerber H. Toxic nodular goitre. *Clin Endocrinol Metab* 1985; 14:351–72

78 Studer H, Gerber H. Toxic multinodular goiter. *In: Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid, 6th ed. Philadelphia: Lippincott* 1991:692–7

79 Berghout A, Wiersinga WM, Smits NJ, Touber JL. The interrelationships between age, thyroid volume, thyroid nodularity and thyroid function in patients with sporadic nontoxic goiter. *Am J Med* 1990;89:602–8

80 Gemsenjäger E, Staub JJ, Girard J, Heitz PH. Preclinical hyperthyroidism in multinodular goiter. *J Clin Endocrinol Metab* 1976;43:810–6

81 Emrich D, Bähre M. Autonomy in euthyroid goitre: maladaptation to iodine deficiency. *Clin Endocrinol (Oxf)* 1978;8:257–65

82 Smeulers J, Docter R, Visser TJ, Hennemann G. Response to thyrotropin-releasing hormone and triiodothyronine suppressibility in euthyroid multinodular goitre. *Clin Endocrinol (Oxf)* 1977;7:389–97

83 Rieu M, Bekka S, Sambor B, Berrod JL, Fombeur JP. Prevalence of subclinical hyperthyroidism and relationship between thyroid hormonal status and thyroid ultrasonographic parameters in patients with non-toxic nodular goitre. *Clin Endocrinol (Oxf)* 1993;39:67–71

84 Elte JWF, Bussemaker JK, Haak A. The natural history of euthyroid multinodular goitre. *Postgrad Med J* 1990;66:186–90

85 Wiener JD. Long-term follow-up in untreated Plummer's disease (autonomous goiter). *Clin Nucl Med* 1987;12:198–203

86 Hay ID, Morris JC. Autonomously functioning thyroid nodules. *In: Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid, 6th ed. Philadelphia: Lippincott* 1991:698–704

87 Thomas GA, Williams D, Williams ED. The clonal origin of thyroid nodules and adenomas. *Am J Pathol* 1989;134:141–7

88 Ramelli F, Studer H, Bruggisser D. Pathogenesis of thyroid nodules in multinodular goiter. *Am J Pathol* 1982;109:215–23

89 Vignaud JM, Duprez A, Bene MC, Leclere J, Faure G, Danchin N, Burlet C. Transplantation of human hyperthyroid tissue to the nude mouse: an experimental model. *Am J Pathol* 1984;117:355–9

90 Sugenoya A, Yamada Y, Kaneko G, Kobayashi M, Miyakawa M, Iida F. In vitro study on release of thyroid hormone in solitary autonomously functioning thyroid nodules using cell culture method. *Endocrinol Japon* 1984;31:749–53

91 Studer H, Peter HJ, Gerber H. Natural heterogeneity of thyroid cells: the basis for understanding thyroid function and nodular goiter growth. *Endocr Rev* 1989; 10:125–35

92 Gerber H, Peter HJ, Studer H, Kaempf LJ. Apparently clonal thyroid adenomas may contain heterogeneously growing and functioning cell subpopulations. *In: Medeiros-Neto GA, Gaitan E, eds. New frontiers in thyroidology, volume 2. New York: Plenum Publishing* 1986:901–5

93 Lyons J, Landis CA, Harsh G, Vallar L, Grünewald K, Feichtinger H, Duh QY, Clark OH, Kawasaki E, Bourne HR, McCormick F. Two G protein oncogenes in human endocrine tumors. *Science* 1990;249:655–9

94 Parma J, Duprez L, Van Sande J, Cochaux P, Gervy C, Mockel J, Dumont J, Vassart G. Somatic mutations in the thyrotropin receptor gene cause hyperfunctioning thyroid adenomas. *Nature* 1993;365:649–51

95 Porcellini A, Ciullo I, Laviola L, Amabile G, Fenzi G, Avvedimento VE. Novel mutations of thyrotropin receptor gene in thyroid hyperfunctioning adenomas. *J Clin Endocrinol Metab* 1994;79:657–61

96 Reinwein D, Benker G, König MP, Pinchera A, Schatz H, Schleusener A. The different types of hyperthyroidism in Europe: Results of a prospective survey of 924 patients. *J Endocrinol Invest* 1988;11:193–200

97 Hamburger JI. Evolution of toxicity in solitary nontoxic autonomously functioning thyroid nodules. *J Clin Endocrinol Metab* 1980;50:1089–93

98 Belfiore A, Sava L, Runello F, Tomaselli L, Vigneri R. Solitary autonomously functioning thyroid nodules and iodine deficiency. *J Clin Endocrinol Metab* 1983; 56:283–7

99 Hamburger JI. Solitary autonomously functioning thyroid lesions: diagnosis, clinical features and pathogenetic considerations. *Am J Med* 1975;58:740–8

100 Blum M, Shenkman L, Hollander CS. The autonomous nodule of the thyroid: correlation of patient age, nodule size and functional status. *Am J Med Sci* 1975; 269:43–50

101 Burman KD, Earll JM, Johnson MC, Wartofsky L. Clinical observations on the solitary autonomous thyroid nodule. *Arch Intern Med* 1974;134:915–9

102 Burman KD. Solitary autonomous thyroid nodules. *Postgrad Med* 1974;56:70–4

103 Skillern PG, McCullagh EP, Clamen M. Radioiodine in diagnosis and therapy of hyperthyroidism. *Arch Intern Med* 1962;110:888–97

104 Miller MJ, Horn RC, Block AM. The evolution of toxic nodular goiter. *Arch Intern Med* 1964;113:122–38

105 Molnar GD, Wilber RD, Lee RE, Woolner LB, Keating FR. On the hyperfunctioning solitary thyroid nodule. *Mayo Clin Proc* 1965;40:665–84

106 Hamburger JI. Should all autonomously functioning thyroid nodules be ablated to prevent the subsequent development of thyrotoxicosis? *In: Hamburger JI, Miller JM, eds. Controversies in Clinical Thyroidology. New York: Springer* 1981:69–105

107 Ashkar FS, Smoak WM. "Owl eye" sign of benign autonomous thyroid nodule. *JAMA* 1970;214:1563

108 Hamilton JG, Lawrence JH. Recent clinical developments in the therapeutic application of radio-phosphorus and radioiodine. *J Clin Invest* 1942;21:624

109 Hertz S, Roberts A. Application of radioactive iodine in the therapy of Graves' disease. *J Clin Invest* 1942;21:624

110 Radionuclide transformations; Energy and intensity of transmissions; 53-iodine-131. *In: ICRP Publication 38. Oxford: Pergamon* 1983:452–3

111 Biological effects of radiation. *In: Parker RP, Smith PHS and Taylor DM, eds. Basic Science of Nuclear Medicine, 1st ed. New York: Longman* 1978:89–116

112 Annex B Biological effects of ionising radiations. Interaction between radiation and matter. *In: ICRP Publication 60. Oxford: Pergamon* 1991:92–9

113 Kennedy JS, Thomson JA. The changes in the thyroid gland after irradiation with ^{131}I or partial thyroidectomy for thyrotoxicosis. *J Pathol* 1974;112:65–81

114 Murray D. The thyroid gland; Effects of ionizing radiation. *In: Kovacs K, Asa SL, eds. Functional Endocrine Pathology, volume 1. Boston: Blackwell* 1991:319–21

115 LiVolsi VA. Fibrosis in the thyroid. *In: Bennington JL, consulting ed. Surgical Pathology of the Thyroid (Volume 22 in the Series Major Problems in Pathology). Philadelphia: Saunders* 1990:98–118

116 Malone JF, Cullen MJ. Two mechanisms for hypothyroidism after ^{131}I therapy. *Lancet* 1976;ii:73–5

117 Saenger EL, Thoma GE, Tompkins EA. Incidence of leukemia following treatment of hyperthyroidism. *JAMA* 1968;205:855–62

118 Holm LE, Hall P, Wiklund K, Lundell G, Berg G, Bjelkengren G, *et al.* Cancer risk after iodine-131 therapy for hyperthyroidism. *J Natl Cancer Inst* 1991;83:1072–7

119 Hall P, Berg G, Bjelkengren G, Boice JD, Ericsson UB, Hallquist A, *et al.* Cancer mortality after iodine-131 therapy for hyperthyroidism. *Int J Cancer* 1992;50:886–90

Chapter

two

Thallium-201 scintigraphy of the suppressed thyroid: an alternative for iodine-123 scanning after TSH stimulation

Published as:

Thallium-201 Scintigraphy of the Suppressed Thyroid: An Alternative for Iodine-123 Scanning After TSH Stimulation

Corstens FHM, Huysmans DAKC, Kloppenborg PWC

Journal of Nuclear Medicine 1988;29:1360–3

Thallium-201 scintigraphy of the thyroid gland suppressed by an autonomous nodule was compared with ^{123}I scintigraphy after TSH stimulation. In all patients, similar images were obtained by both methods. In 20 patients, the contralateral lobe was visualized on both scans and in 14 of these, the upper pole of the ipsilateral lobe was also visualized. In one patient, neither ^{123}I scanning after TSH nor ^{201}Tl scintigraphy showed any extranodular tissue. This study suggests that ^{201}Tl scintigraphy is a reliable alternative for scanning after TSH. It is a relatively simple method, not inducing any TSH-related allergic reactions. Iodine uptake in extranodular tissue is not stimulated and therefore, ^{201}Tl scintigraphy and radioiodine therapy can be combined on one day, without increasing the risk of radiation damage to the normal thyroid tissue with a resultant post-treatment hypothyroidism.

2.1 Introduction

The solitary autonomous thyroid nodule is "a discrete nodular structure with function both independent of pituitary stimulation and unrelated to that of the remaining thyroid tissue" [1]. It is suspected when palpation of the neck reveals a single nodule and preliminary iodine-scintigraphy shows a hot nodule. Other possibilities to differentiate from are thyroidal anomalies such as thyroid hemigenesis. Therefore, the diagnosis of a solitary autonomous thyroid nodule depends upon the visualization of suppressed extranodular thyroid tissue.

Stimulation of iodine uptake in the suppressed tissue by thyroid-stimulating hormone (TSH) leads to visualization of the suppressed parts on iodine-scintigraphy. TSH stimulation, however, has considerable disadvantages. The bovine proteins may induce allergic reactions either systemic or local [2]. It is a time-consuming investigation because of the need of intramuscular TSH injections. On top of this, TSH is no longer available in regular pharmacies in The Netherlands. The production was stopped by the manufacturer because of low demand.

Ultrasonography is another method to visualize thyroid tissue. However, it does not provide any physiological information. A lobe may be present but nonfunctional because of a number of reasons. Ultrasonography can only give additional information provided that it is performed by a radiologist with ample experience and having at his disposal a special transducer for superficial structures.

The use of thallium-201 (^{201}Tl) for diagnosis and follow-up of thyroid carcinoma is well established. In 1979, Fukuchi *et al.* [3] reported significant thallium uptake in patients with various diseases causing thyroid enlargement. In 1984, Müller-Brand *et al.* [4] proposed ^{201}Tl scintigraphy as a new way to visualize suppressed tissue in benign thyroid diseases.

In our clinic from October 1985 onward ^{201}Tl scintigraphy as well as iodine-123 (^{123}I) scintigraphy after TSH stimulation were performed in all patients presenting with a hot nodule on ^{123}I scintigraphy. The purpose of the study was to investigate the quality of ^{201}Tl scintigraphy as an alternative for scanning after TSH stimulation.

2.2 Materials and methods

Twenty one patients, 17 women and 4 men aged 59.5 ± 12.8 yr (mean $\pm$ SD), were studied prospectively. Biochemical manifestations of hyperthyroidism were present in every patient. Serum levels of thyroxine were 178 ± 19 nmol/l

(normal range 54–154 nmol/l), of free thyroxine 38 ± 24 pmol/l (normal range 9–17 pmol/l), of triiodothyronine 3.9 ± 0.6 nmol/l (normal range 1.5–3.5 nmol/l). In all patients the serum TSH level was <0.2 mU/l (normal range 0.4–4.0 mU/l). The 3-hour thyroid ^{131}I uptake was 32% ± 14% (normal range 5%–30%).

Scintigraphic methods

Baseline Iodine-123 scan

0.7 mCi (30 MBq) of [^{123}I]sodium iodide (high purity ^{123}I) were injected intravenously. One hour later, the thyroid region was imaged in the anterior and in the right and left oblique position using a gamma camera (Picker Dyna camera 4/15) with a pinhole collimator. Antithyroid drugs, if used, were stopped at least 2 days previously.

Thallium-201 scan

Carried out 1 to 14 days after baseline ^{123}I scintigraphy and 1 week before TSH stimulation. 2 mCi (74 MBq) of [^{201}Tl]thallous chloride were injected intravenously. Fifteen minutes later scintigraphy of the neck from the anterior view followed. A converging collimator was used because its efficiency is five times as high as that of the pinhole collimator.

Iodine-123 scan after TSH stimulation

On three subsequent days 10 IU of TSH were injected intramuscularly. On the third day, 1 hour after the intravenous administration of 0.7 mCi (30 MBq) of ^{123}I, an anterior image of the thyroid region was obtained.

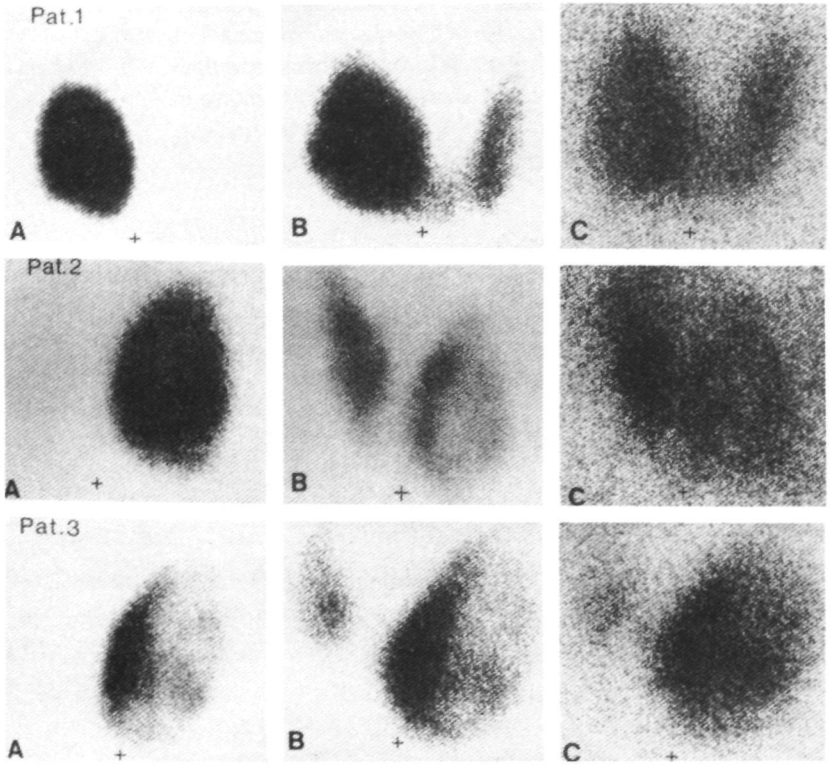
The surface of each nodule on the baseline ^{123}I scan was measured planimetrically. In order to estimate the real size of the nodules (in cm^2) the obtained values were corrected for diminution caused by the pinhole collimator using the known distance between two radioactive markers as a reference.

Comparing the sizes of the lobes on both scans was not attempted because of the use of two collimators, causing different and not very reliable factors of diminution. For that reason, only the presence of a contralateral lobe and the visibility of the upper or lower pole of the ipsilateral lobe (not shown on the baseline ^{123}I scan) were accounted for as evidence of the visualization of suppressed thyroid tissue.

2.3 Results

In all patients the baseline ^{123}I scan showed a hot nodule with suppression of supposedly remaining thyroid tissue. The size of the nodules was 16 ± 5 cm^2 (mean $\pm$ SD). The nodules did not necessarily have a homogeneous uptake.

Figure 2.1 *Visualization of the thyroid (anterior view) in three patients with a solitary autonomous thyroid nodule with ^{123}I (A), with ^{123}I after 3 days of 10 IU of TSH i.m. (B) and with ^{201}Tl (C). Patient 1 (upper row): Equal uptake in the nodule and extranodular tissue. Patient 2 (middle row): Higher uptake in extranodular tissue compared to the nodule. Patient 3 (lower row): Non-uniform uptake in the nodule and lower uptake in extranodular tissue compared to the nodule. + represents sternal notch*



In twenty of the patients the ^{123}I scan after TSH stimulation visualized previously suppressed extranodular thyroid tissue. These patients were considered to have a solitary autonomous thyroid nodule. In 17 out of 20 patients the nodule was clearly localized in the lower pole of the lobe. In three patients no differentiation between lower and upper pole was possible. In one hyperthyroid patient with a hot nodule on baseline ^{123}I scintigraphy, the ^{123}I scintigraphy after TSH stimulation showed no extranodular tissue.

Examples of the scans in three patients are shown in Figure 2.1. On visual interpretation of the scans the sizes of the lobes both on ^{201}Tl scintigraphy and on ^{123}I scintigraphy after TSH were similar. In all 20 patients with a solitary autonomous thyroid nodule the contralateral lobe was visible on the ^{201}Tl scan as well as on the ^{123}I scan after TSH stimulation. The upper pole of the ipsilateral lobe was visualized with both methods in 14 patients. Both ^{201}Tl scans and ^{123}I scans after TSH stimulation provided sufficient visualization of the thyroid gland, including the previously suppressed tissue. Delineation of the thyroid gland was slightly better on ^{123}I scintigraphy after TSH in ten patients. In nine patients the images were equal and in one case the ^{201}Tl scan proved to be superior. In 17 patients the tracer uptake in the nodule was similar to that in the surrounding thyroid tissue, on the thallium-scan as well as on the iodine-scan after TSH. In three patients the tracer uptake in the nodule was significantly higher than that in the extranodular tissue on both scans. Photopenic zones in the nodule, already visible on baseline ^{123}I scintigraphy, were seen on both scans in 12 patients.

In the patient with a hot nodule on the baseline ^{123}I scan, in whom ^{123}I scintigraphy after TSH stimulation did not show extranodular thyroid tissue, the ^{201}Tl scintigraphy was in complete agreement with this finding, as was ultrasonography.

2.4 Discussion

This study emphasizes that suppressed thyroid tissue in patients with a solitary autonomous thyroid nodule can be visualized by ^{201}Tl scintigraphy equally well as by ^{123}I scintigraphy after TSH stimulation. In this series an upper pole and a contralateral lobe were seen on both scans with the same frequency and always in the same patients. The target to non-target ratio was unequivocally better in iodine-scintigraphy after TSH stimulation. Nevertheless there was a good delineation of the thyroid tissue on ^{201}Tl scans too. In one patient with a hot nodule on a baseline ^{123}I scan neither ^{201}Tl scintigraphy nor ^{123}I scintigraphy

after TSH stimulation showed any extranodular tissue. Ultrasonography findings were in agreement with the scintigraphic observations. This patient in all probability has agenesia of one thyroid lobe.

The female preponderance in our series has also been observed in other studies on solitary autonomous thyroid nodules [1, 4]. The older age and hyperthyroid state of our patients as well as the relatively large size of the nodules in our series are in accordance with the natural history of solitary autonomous thyroid nodules. Hyperthyroidism in patients with a solitary autonomous thyroid nodule is seen more often in elderly people with larger nodules [1, 5]. In 17 out of 20 patients the nodule was clearly localized in the lower pole of the lobe. We could not find a convincing explanation for the observed preferential localization of hot nodules in the lower part of the thyroid.

Thallium uptake in the thyroid has been assumed to depend upon a factor other than mere blood flow. Thallium forms a gradient in thyroid tissue which is similar to the gradient of potassium and which is probably mediated by Na^+-K^+ ATPase, since it can be inhibited by ouabaine and potassium [6]. Thallium uptake is not inhibited by perchlorate, indicating that the anionic side of the iodide pump is not used in concentrating thallium [7]. Our study is in accordance with these findings, for in 17 scans uptakes in the nodule and in the surrounding thyroid tissue in which the iodide trapping mechanism was suppressed were equal. In only three out of 20 ^{201}Tl scans the extranodular tissue showed less activity than the nodule. Photopenic zones in the nodules can probably be accounted for by cystic degeneration of the nodules [1, 8]. Some authors [6, 9] concluded that the entry not only of anions such as iodide, but also of cations, for example thallium, is controlled by TSH. Others could not prove a statistically significant correlation between TSH stimulation and thallium uptake [3, 7]. In our study ^{201}Tl scans were performed in patients with low serum concentrations of TSH (<0.2 mU/l) and prior to exogenous TSH administration. Therefore, the clear imaging of thyroid tissue resulting from sufficient ^{201}Tl uptake suggests that TSH is not a major determinant of thallium uptake.

Every method has its pitfalls. Unilateral thyroiditis, a rare occurrence in our area, may mimic a solitary autonomous thyroid nodule: ^{123}I uptake is limited to one lobe (the contralateral lobe) on the preliminary ^{123}I scan and the complete thyroid gland is visualized on ^{201}Tl scintigraphy. Therefore, additional information like radioactive iodine uptake, search for thyroid antibodies and erythrocyte sedimentation rate is still not superfluous.

On the basis of this study we conclude that ^{201}Tl scintigraphy can be used to visualize suppressed thyroid tissue in patients with a "hot" nodule on preliminary ^{123}I scintigraphy. A disadvantage of this technique, compared to ultrasonography, is the radiation burden. The effective dose equivalent from 74 MBq

of ^{201}Tl is 7 mSv, compared to 5 mSv from 30 MBq of ^{123}I [10]. However, most of these patients will subsequently be treated with a high dose of radioactive iodine.

There are some considerable advantages of ^{201}Tl scintigraphy over ^{123}I scanning after TSH. It does not induce systemic or local allergic reactions which can be caused by bovine TSH, and it can be performed without discontinuation of antithyroid drug therapy. Furthermore, a therapeutic dose of radioiodine (^{131}I) can be administered immediately after ^{201}Tl scintigraphy since iodine uptake in the extranodular tissue has not been stimulated. After TSH stimulation radioiodine treatment should be postponed for several weeks in order to reduce the chance of post-treatment hypothyroidism due to TSH stimulation of the extranodular tissue. In fact, suppression of the extranodular tissue has to be ascertained again immediately before the administration of the therapeutic ^{131}I dose. The use of ^{201}Tl scintigraphy enables one physician in one department of nuclear medicine to combine reliable diagnostics and ^{131}I therapy in a short space of time. Thallium-201 scintigraphy can be performed in approximately one-half hour by a laboratory assistant. This makes it a relatively simple investigation, whereas ultrasonography can only be performed in a hospital having a specialist with experience in thyroid imaging at its disposal. Most departments of nuclear medicine doing cardiac examinations with radio-thallium have ^{201}Tl readily available.

Acknowledgment

The authors thank Mr. Wim van den Broek, Department of Nuclear Medicine, for technical assistance.

2.5 References

1 Hamburger JI. Solitary autonomously functioning thyroid lesions. Diagnosis, clinical features and pathogenetic considerations. *Am J Med* 1975;58:740–8

2 Krishnamurthy GT. Human reaction to bovine TSH. Concise communication. *J Nucl Med* 1978;19:284–6

3 Fukuchi M, Kido A, Hyodo K, *et al.* Uptake of thallium-201 in enlarged thyroid glands: concise communication. *J Nucl Med* 1979;20:827–32

4 Müller-Brand J, Staub JJ, Fridrich R. Die Thalliumszintigraphie der Schilddrüse als Alternativverfahren zum Nachweis von funktionell stillgelegtem Schilddrüsengewebe. *Schweiz Med Wochenschr* 1984;114:1686–9

5 Blum M, Shenkman L, Hollander CS. The autonomous nodule of the thyroid: correlation of patient age, nodule size and functional status. *Am J Med Sci* 1975; 169:43–50

6 Mayaan ML, Volpert EM, Fine EJ, *et al.* Thyroid uptake of ^{201}thallium and its control by TSH. *Acta Endocrinol (Copenh)* 1981;97:461–5

7 Oster ZH, Strauss HW, Harrison K, *et al.* Thallium-201 distribution in the thyroid: relationship to thyroidal trapping function. *Radiology* 1978;126:733–4

8 Ashkar FS, Smoak W. "Owl eye" sign of benign autonomous thyroid nodule. *JAMA* 1970;214:1563

9 Solomon DH. Effects of thyrotropin on thyroidal water and electrolytes in the chick. *Endocrinology* 1961;69:939–57

10 Johansonn L, Mattson S, Nosslin B. Effective dose equivalents from radiopharmaceuticals. *Eur J Nucl Med* 1984;9:485–9

Chapter three

Long-term follow-up in toxic solitary autonomous thyroid nodules treated with radioactive iodine

Published as:

Long-term Follow-up in Toxic Solitary Autonomous Thyroid Nodules Treated with Radioactive Iodine

Huysmans DAKC, Corstens FHM, Kloppenborg PWC

Journal of Nuclear Medicine 1991;32:27–30

The long-term effects of radioiodine treatment on thyroid function in patients with a toxic solitary autonomous thyroid nodule were evaluated. Fifty-two patients received a therapeutic dose of 20 mCi of iodine-131 (^{131}I). Duration of follow-up was 10 ± 4 yr. Follow-up data included a biochemical evaluation of thyroid function. The failure rate (recurrent hyperthyroidism) was 2%. The incidence of hypothyroidism was 6% and was not related to the dose per gram of nodular tissue. Oral administration of 20 mCi of radioiodine is a simple and highly effective method for the treatment of patients with a toxic autonomous thyroid nodule. The risk of development of hypothyroidism is low if extranodular uptake of ^{131}I is prevented. This can be achieved by not treating euthyroid patients, by no longer using injections of exogenous thyroid-stimulating hormone in the diagnostic work-up of the patients and by always performing radioiodine imaging shortly before treatment.

3.1 Introduction

Two subgroups of nodular thyroid diseases with autonomous hyperfunction are currently recognized as clinically distinct entities. Toxic multinodular goiter is a disease in which there is a large multinodular goiter. It predominantly afflicts elderly people. The goiter and autonomous function often precede the onset of hyperthyroidism by many years [1]. Goetsch's disease or the solitary autonomous thyroid nodule is characterized by a single thyroid adenoma which is functioning autonomously and independently of pituitary stimulation or any other extrathyroidal stimulator. The thyroid hormone secreted by the nodule has a negative feedback on the production of thyroid-stimulating hormone (TSH) by the pituitary gland. By this mechanism, the function of the TSH-dependent extranodular tissue is suppressed to a variable degree [1].

Many patients with a solitary autonomously functioning thyroid nodule are euthyroid. Progression to persisting hyperthyroidism occurs in only a small number of patients. Moreover, spontaneous degeneration of the nodule is possible [2]. Therefore, non-toxic autonomous thyroid nodules are regularly left untreated in The Netherlands.

Radioactive iodine is a generally accepted method for the treatment of hyperthyroidism, especially in patients with a solitary autonomous thyroid nodule. Post-treatment hypothyroidism seems less likely if iodine uptake in the extranodular thyroid tissue is sufficiently suppressed, which means that the nodule is the only visible thyroid tissue on iodine scintigraphy.

There are few reports on the long-term follow-up of patients with hyperthyroidism, due to a solitary autonomous thyroid nodule, treated with iodine-131 (^{131}I) [3–9]. Recently, we have studied the long-term effects of radioiodine treatment on thyroid function in patients with hyperthyroidism due to Goetsch's disease treated in our hospital.

3.2 Patients and methods

Iodine-131 therapy

Between 1970 and 1985, 52 patients with a solitary autonomous thyroid nodule received an oral standard therapeutic dose of 20 mCi (740 MBq) of ^{131}I as sodium iodide at the University Hospital, Nijmegen. The female-to-male ratio was 3.3 : 1 and the age range was 58.2 ± 11.2 yr (mean ± SD). All patients had clinical signs and symptoms of hyperthyroidism as well as elevated levels of thyroid hormones (thyroxine (T_4) 186 ± 44 nmol/l, triiodothyronine (T_3) 4.3 ± 1.1 nmol/l). The 24-h

thyroid ^{131}I uptake was 52% ± 12%. Thyroid scans using [^{131}I]sodium iodide, [^{123}I]sodium iodide or (in 9 patients) technetium-99m-pertechnetate showed single hot nodules with total suppression of extranodular tissue in 48 patients and near-total suppression in four. The weight of the nodules was estimated from the thyroid scan using the formula: $\frac{1}{6}\pi xy^2$ where x is the longest and y is the shortest diameter of the nodule. For each nodule, the total ^{131}I dose delivered was divided by this estimated nodular weight and multiplied by the fractional 24-h ^{131}I uptake in order to calculate the ^{131}I dose per gram of functional thyroid tissue [6]. Iodine scintigraphy after injections of exogenous TSH was used to visualize extranodular thyroid tissue. Therapy was postponed for at least 4 days after imaging with TSH stimulation. Twelve patients were on antithyroid medication (thiamazole) prior to ^{131}I therapy. They concomitantly used a thyromimetic drug to avoid elevation of the serum TSH level. The antithyroid drug was discontinued for at least three days prior to ^{131}I administration till three days afterwards.

In our laboratory, normal values for the various tests used are: serum T_4 65–140 nmol/l, serum T_3 1.8–2.9 nmol/l, serum free T_4 9–19 pmol/l, serum TSH 0.4–4.0 mU/l, and 24-h ^{131}I uptake 10%–59%.

Follow-up

The patients were followed for a period of 4–17.5 yr (mean 10 ± 4 yr). Five of them had died of unrelated causes and one patient had emigrated. The last available data from the medical records of these patients were used. All other patients were seen by their own physician or by ourselves. A short medical interview and physical examination were carried out. Serum T_4 and TSH levels were measured utilizing standard methods. Criteria for hyperthyroidism were a serum T_4 level over 140 nmol/l together with a suppressed TSH. Hypothyroidism was diagnosed in patients with a serum T_4 level of less than 65 nmol/l together with a serum TSH level over 4.9 mU/l. In patients with an elevated TSH, the serum free T_4 level was also measured.

3.3 Results

All 52 patients became euthyroid within 6 months after radioiodine therapy and antithyroid medication was stopped. In one patient, thyrotoxic symptoms recurred 1.5 yr later. Iodine scintigraphy showed the same hot nodule. This patient was successfully treated with a second dose of 20 mCi of ^{131}I. Hyperthyroidism did not recur in any of the other patients.

During the follow-up period, thyroxine therapy was started in six patients. In two of these patients, therapy was started 3 and 7 yr after radioiodine therapy because of mild clinical and biochemical hyperthyroidism (T_4 level, 56 and 58 nmol/l, respectively; TSH level, 16.9 and 19.1 mU/l, respectively). In a third patient, thyroxine therapy was started in another hospital after 15 yr (no further data available). Two other patients became hypothyroid (T_4 level 42 and 60 nmol/l, respectively; TSH level 54 and 33 mU/l, respectively) 2 and 6 yr after they had been treated with ^{131}I. However, they had been treated at an inappropriate moment, while the effects of the injected exogenous TSH were still present. In the sixth patient, thyroxine therapy was started unnecessarily after 3 yr (serum TSH level at the start of thyroxine therapy 1.4 mU/l). The remaining 46 patients, including the patient who had received 20 mCi twice, were, without replacement therapy, clinically and biochemically euthyroid at the end of the follow-up period. Of these patients, six had a slightly elevated serum TSH level (5.2–8.1 mU/l) together with a normal serum T_4 level (80–102 nmol/l), and free T_4 level (8.6–11.5 pmol/l).

The development of hypothyroidism in our series was not related to the dose per gram of nodular tissue corrected for radioiodine uptake (399 ± 242 μCi/g in the 46 patients who remained euthyroid and 408 ± 295 μCi/g in the six patients who became hypothyroid ($p \geq 0.10$, Wilcoxon's test). No antithyroid antibodies were present in the patients in whom hypothyroidism developed. The prior use of antithyroid medication, stopped at least three days before ^{131}I administration, in 12 patients, seems not to have influenced the development of hypothyroidism. One of these patients became hypothyroid. This patient had a suppressed serum TSH level on the day of therapy.

In order to reveal a process of slowly diminishing thyroid function after radioiodine therapy, we compared serum T_4 levels as measured in 1984 and 1988 in 29 patients who had not become hypothyroid. In 1984, the T_4 level was 90 ± 21 nmol/l, in 1988 93 ± 19 nmol/l ($p \geq 0.10$, Wilcoxon's test). None of these patients showed a decline of the serum T_4 level.

3.4 Discussion

In the present study, patients with a solitary autonomous thyroid nodule were treated with radioiodine only when they were clinically and biochemically hyperthyroid. The high mean age (58.2 ± 11.2 yr), the suppression of extranodular tissue, and the rather large size of most nodules are in accordance with the hyperthyroid state [1, 2, 10–12].

All of our 52 patients became euthyroid within 0.5 yr after a standard dose of 20 mCi of ^{131}I and during a mean follow-up of 10 yr hyperthyroidism recurred in only one patient. This patient received a second dose of 20 mCi of ^{131}I 1.5 yr after the first dose. The failure rate found in our study (2%) is lower than that found in the study of Ratcliffe *et al.* [8]. In their study, hyperthyroidism recurred in 7 of 48 patients after a standard oral dose of 15 mCi of ^{131}I. Other authors [3, 4, 6, 7, 13] not using a standard dose, but a dose adjusted according to the individual size of the nodule, also reported higher incidences of therapy failures (7%–52%; Table 3.1).

Table 3.1 *Failure rate of ^{131}I therapy in patients with solitary autonomous thyroid nodules and hyperthyroidism (primary therapy failures and recurrences)* *

Author	Nr. of pat.	Failure rate	Follow-up (yr)		Method of calculation	Dose of ^{131}I (mCi)
Fontana	23	52%	Life-table		200–800 Gy	?
Heinze	188	9%	$2.5 \pm ?$		300–400 Gy	18.9 ± 9.6
Hegedüs	27	7%	1 (all patients)		100 μCi/g	$7.5 \pm ?$
Mariotti	138	15%	3.2 ± 2.2	(1–11)	180 μCi/g	12.6 ± 4.1
Ratcliffe	48	15%	$3.1 \pm ?$	(2–10)	Standard dose	15
Ross	45	13%	4.9 ± 3.2	(0.5–13.5)	160 μCi/g	$10.3 \pm ?$
This study	52	2%	10 ± 4	(4.0–17.5)	Standard dose	20

* Mean ± SD (range)
? Not mentioned

During the follow-up period, thyroxine therapy was started in 6 of our 52 patients. However, in one of these patients thyroxine therapy was started while the patient was not hypothyroid. In two patients, treatment with ^{131}I was given while the effects of injected exogenous TSH were still present. Excluding these three patients the incidence of hypothyroidism in our series is 3/49 or 6%. Other investigators found similarly low percentages, although during shorter follow-up periods. Mariotti *et al.* [7] reported five cases of hypothyroidism after treatment of 126 patients with a dose of 180 μCi of ^{131}I per gram of nodular tissue (duration of follow-up 3.2 ± 2.2 yr). Eyre-Brooke *et al.* [14] found two cases of hypothyroidism out of 37 patients treated

with 1.2–15 mCi of ^{131}I (mean duration of follow-up 6.5 yr) while none of the 48 patients of Ratcliffe *et al.* [8] developed hypothyroidism after treatment with 15 mCi of ^{131}I (mean duration of follow-up 3.1 yr, range 2–10 yr).

In two studies, rather high incidences of hypothyroidism have been reported. In the study of Goldstein *et al.* [5], 8 of 22 patients became hypothyroid after treatment with 15–55 mCi of radioiodine. However, it has to be noted that 16 of these patients were euthyroid at the time of treatment and 12 of them had incomplete suppression of uptake in the extranodular tissue. Fontana *et al.* [4] reported an incidence of hypothyroidism of 17% at 10 yr and 44% at 20 yr after treatment of 29 patients with 20,000–80,000 rads (these authors used a life table method). But none of their patients who had (almost) complete suppression of the function of the extranodular parenchyma developed hypothyroidism.

One might think that the amount of administered ^{131}I plays a major role in the development of hypothyroidism after radioiodine treatment in thyrotoxic patients with a solitary autonomous thyroid nodule. However, the data in our study and in those of Goldstein *et al.* [5] and Fontana *et al.* [4] strongly suggest that it is not the dose of radioiodine but the presence of incomplete suppression of iodine uptake in the extranodular tissue that determines the incidence of hypothyroidism. Extranodular iodine uptake is, of course, frequently seen in patients with a solitary autonomous thyroid nodule who are not thyrotoxic. In order to prevent the development of hypothyroidism, radioiodine treatment should not be given to these patients. Incomplete suppression of uptake in extranodular tissue is also present after exogenous TSH injections, sometimes even months afterwards. Therefore, to visualize extranodular thyroid tissue, we recommended imaging with thallium-201-chloride or ultrasonography of the thyroid instead of imaging with ^{131}I after pretreatment with injections of exogenous TSH [15]. The latter procedure is no longer in use in The Netherlands. In our opinion, visualization of suppressed normal thyroid tissue is relevant. If suppressed extranodular tissue is present, we assume that this parenchyma will take over thyroid function after ablation of the nodule with a relatively high dose of 20 mCi of ^{131}I. If there is no extranodular tissue, we routinely administer a lower dose calculated according to the method described by DeGroot [16] in order to diminish the risk of post-treatment hypothyroidism.

We conclude that oral administration of 20 mCi of radioiodine is a simple and highly effective method for the treatment of patients with a toxic autonomous thyroid nodule. The risk of development of hypothyroidism is low if the uptake of ^{131}I in the extranodular tissue is prevented. This can be done by not treating euthyroid patients, by no longer using injected exogenous

TSH in the diagnostic work-up of the patients, and by always performing radioiodine imaging immediately before treatment. When this pretreatment radioiodine image reveals uptake of iodine in extranodular parenchyma, therapy has to be postponed.

3.5 References

1 Hamburger JI. The autonomously functioning thyroid nodule: Goetsch's disease. *Endocr Rev* 1987;8:439-47

2 Hamburger JI. Solitary autonomously functioning thyroid lesions: Diagnosis, clinical features, and pathogenetic considerations. *Am J Med* 1975;58:740-8

3 Heinze H, Pfeiffer K, Lichtenstein Z. Radiojodtherapie des autonomen Adenoms. *Dtsch Med Wochenschr* 1975;100:2203–8

4 Fontana B, Curti G, Biggi A, Fresco G. The incidence of hypothyroidism after radioactive iodine therapy for autonomous hyperfunctioning thyroid nodules evaluated by means of life-table method. *J Nucl Med All Sci* 1980;24:85-91

5 Goldstein R, Hart IR. Follow-up of solitary autonomous thyroid nodules treated with ^{131}I. *N Engl J Med* 1983;309:1473–1476

6 Ross D, Ridgway C, Daniels G. Successful treatment of solitary toxic thyroid nodules with relatively low-dose iodine-131 with low prevalence of hypothyroidism. *Ann Intern Med* 1984;101:488–90

7 Mariotti S, Martino E, Francesconi M, *et al.* Serum thyroid autoantibodies as a risk factor for development of hypothyroidism after radioactive iodine therapy for single thyroid 'hot' nodule. *Acta Endocrinol (Copenh)* 1986;113:500–7

8 Ratcliffe G, Cooke S, Fogelman I, Maisey M. Radioiodine treatment of solitary functioning thyroid nodules. *Br J Radiol* 1986;59:385–7

9 Corstens F, Smals A, Buys W, Kloppenborg P. Letter to the editor. *N Engl J Med* 1984;310:1393

10 Skillern P, McCullagh E, Clamen M. Radioiodine in diagnosis and therapy of hyperthyroidism. *Arch Intern Med* 1962;110:888–97

11 Blum M, Shenkman L, Hollander CS. The autonomous nodule of the thyroid: correlation of patient age, nodule size, and functional status. *Am J Med Sci* 1975; 169:43–50

12 Burman K, Earl J, Johnson M, Wartofsky L. Clinical observations on the solitary autonomous thyroid nodule. *Arch Intern Med* 1974;134:915–9

13 Hegedüs L, Veiergang D, Karstrup S, Hansen J. Compensated ^{131}I-therapy of solitary autonomous thyroid nodules: effect on thyroid size and early hypothyroidism. *Acta Endocrinol (Copenh)* 1986;113:226–32

14 Eyre-Brooke IA, Talbot CH. The treatment of autonomous functioning thyroid nodules. *Br J Surg* 1982;69:577–9

15 Corstens F, Huysmans D, Kloppenborg P. Thallium-201 scintigraphy of the suppressed thyroid: an alternative for iodine-123 scanning after TSH stimulation. *J Nucl Med* 1988;29:1360–3

16 DeGroot LJ. Graves' disease diagnosis and treatment. Multinodular goiter. *In: DeGroot LJ, Stanbury JB, eds. The Thyroid and Its Diseases, 4th ed. New York: Wiley* 1975 : 314–67 and 637–65

Chapter four

Long-term results of two schedules of radioiodine treatment for toxic multinodular goiter

Published as:

Long-Term Results of Two Schedules of Radioiodine Treatment for Toxic Multinodular Goitre

Huysmans DAKC, Hermus ARMM, Corstens FHM,
Kloppenborg PWC

European Journal of Nuclear Medicine 1993;20:1056–62

The long-term effects of two schedules of radioiodine therapy in patients with toxic multinodular goiter were evaluated. Forty-five patients (group A) were treated with low doses and fifty-eight patients (group B) with calculated doses adjusted for thyroid weight (1.85–3.70 MBq/g) and radioactive iodine uptake. Follow-up (mean ± SEM) was 4.3 ± 0.2 years and 5.2 ± 0.3 years, respectively ($p > 0.1$). At the end of follow-up, hyperthyroidism was successfully reversed in 73% (group A) and 88% (group B). In each group, hypothyroidism was present in 7%. The total dose per gram of thyroid tissue was not significantly different in groups A and B (2.1 ± 0.2 versus 2.7 ± 0.2 MBq/g). However, for patients treated with calculated doses the number of ^{131}I administrations was significantly lower (1.3 ± 0.1) than for patients treated with low doses (2.2 ± 0.2), and the percentage of patients who were adequately treated with a single dose was more than twice as high (66% in group B versus 27% in group A). Euthyroidism was reached within a significantly shorter time after treatment with calculated doses (median time 0.6 years in group B versus 1.5 years in group A; life table analysis). It is concluded that radioiodine is an effective treatment for toxic multinodular goiter with a low risk of post-treatment hypothyroidism and that calculated (higher) doses appear to be preferable to low doses.

4.1 Introduction

Since the early 1940s, radioactive iodine has frequently been administered to patients with hyperthyroidism. In earlier reports on the results of this treatment, different types of thyrotoxicosis were not distinguished. Later studies on radioiodine therapy of Graves' disease showed that regardless of the dosage schedule used, patients with Graves' disease are at high risk of becoming hypothyroid [1–2]. In studies on the results of radioiodine treatment of patients with toxic uni- and multinodular goiters, incidences of hypothyroidism are extremely varied, ranging from 1% to 64% [3–20]. However, interpretation of literature data is difficult for several reasons. First, some studies do not differentiate between toxic multinodular goiter and toxic solitary autonomous thyroid nodules [4–6, 8, 14]. In one study, even patients with Graves' ophthalmopathy were not excluded [4]. Second, sometimes only palpation is used to determine thyroid nodularity and weight [3–8, 19]. Moreover, in many reports duration of follow-up is not exactly stated [3–7, 10, 11, 13]. Therefore, we studied the results of radioiodine treatment in patients with toxic multinodular goiter treated in our hospital. Criteria for hyperthyroidism, multinodularity and absence of ophthalmopathy were strictly defined. Two different dosage schedules have been used in recent years. In the first regimen, low doses, irrespective of thyroid weight and thyroid radioactive iodine uptake, were administered. In the second, doses were adjusted for thyroid weight and radioactive iodine uptake. The long-term results of these two dosage schedules were evaluated and compared with studies in the literature with respect to duration of therapy, remission of hyperthyroidism and incidence of hypothyroidism.

4.2 Patients and methods

Patients

One hundred and three patients with toxic multinodular goiter treated with radioactive iodine were studied. Only patients with a follow-up of more than 6 months after the first dose of iodine-131 (^{131}I), given between 1979 and 1990, were included. Four patients had had adverse reactions on antithyroid drugs, necessitating early termination of drug treatment. In all other patients, previous therapy with antithyroid drugs for at least 6 months had not resulted in a permanent remission of hyperthyroidism.

The diagnosis of hyperthyroidism was based on clinical evaluation and laboratory tests including serum levels of thyroid-stimulating hormone (TSH), thyroxine (T_4), triiodothyronine (T_3) and free thyroxine (fT_4).

The diagnosis of multinodular goiter was based on the presence of one or more thyroid nodules at palpation and an irregular distribution of ^{123}I or ^{131}I as sodium iodide or technetium-99m pertechnetate on a thyroid scan. Patients with a solitary hot nodule were excluded, as were patients with signs of Graves' ophthalmopathy.

Radioiodine treatment schedules

Patients were offered two forms of radioiodine treatment: low doses without regard to individual variables such as thyroid radioiodine uptake (RAIU) and thyroid weight (on an out-patient basis) or calculated doses adjusted for thyroid weight and thyroid RAIU (on an in-patient basis for those who received >150 MBq). There was a tendency for larger goiters to be treated with calculated doses.

Forty-five patients were treated with low doses. The first therapeutic dose was 150 MBq of ^{131}I. Antithyroid drugs were not taken for at least three days before and after therapy. The effect of the first dose was evaluated 6 months later. For patients who were not treated with antithyroid drugs, a second low dose of ^{131}I (150 MBq) was given to those who were still clinically and biochemically thyrotoxic. For patients on antithyroid drugs, a second dose of ^{131}I (150 MBq) was administered to those who still had an elevated thyroid RAIU, measured 3 hours after oral ingestion of 0.37 MBq of ^{131}I (3-h RAIU, normal range 5%–30%), after stopping the antithyroid drug for at least 3 days. If the 3-h RAIU was ≤30%, antithyroid medication was stopped and ^{131}I therapy was only repeated if the patient became clinically and biochemically thyrotoxic again during subsequent follow-up. The effect of the second and of every subsequent dose of ^{131}I was evaluated 6 months later, using the same parameters as with the first dose. A possible third or fourth dose was also 150 MBq. Exceptions were four patients who received 300 MBq as the third or fourth dose. Two patients were treated more than four times: in one patient the dose was doubled after five doses of 150 MBq (two times 300 MBq) and one patient received six doses of 150 MBq of radioiodine. In this dosage schedule, the radiation absorbed dose per treatment was far below 100 Gy in all patients.

The second option, administration of a calculated dose of radioiodine, was used for 58 patients. The administered dose was calculated according to the method described by DeGroot [21], which is based on two variables (thyroid weight and RAIU) and on the use of a higher retained dose per gram of thyroid tissue for larger glands. Thyroid weight was estimated from the planimetric surface on the thyroid scan using the formula of Doering: thyroid weight = $0.326 \times (\text{surface})^{3/2}$ [22]. Thyroid RAIU was measured 24 hours after oral ingestion of 0.37 MBq of ^{131}I (24-h RAIU, normal range 10%–59%). The

retained dose at 24 hours ranges from 1.85 MBq (50 μCi)/g for thyroids weighing less than 40 g to 3.70 MBq (100 μCi)/g for thyroids weighing more than 100 g. The following formula was used:

$$\text{administered activity (GBq)} = \frac{\text{thyroid weight (g)} \times (1.85\text{–}3.7)\text{MBq/g}}{\text{24-h RAIU(\%)} \times 10}$$

Assuming an effective half-life of ^{131}I of 6 days [21], radiation absorbed doses in this dosage schedule ranged from 50 Gy per treatment in thyroids weighing less than 40 g to 100 Gy in thyroids weighing more than 100 g.

Six months after the first dose, the effect was evaluated using the parameters mentioned in the scheme of low doses. If further treatments were needed, calculated doses were again administered.

Follow-up after radioiodine therapy

Endpoint analysis

All living patients (n = 94) were invited for a single visit to our hospital in February 1992. A short medical interview and physical examination were performed and blood samples were obtained. Serum TSH, T_4, T_3 and fT_4 levels were measured using standard methods. Normal values for our laboratory are: TSH (fluoroimmunoassay, Delfia hTSH, Pharmacia) 0.40–4.00 mU/l, T_4 (radioimmunoassay, Amerlex-M T4) 54–154 nmol/l, T_3 (radioimmunoassay, Amerlex-M T3) 1.5–3.5 nmol/l and fT_4 (SPAC ET.FT4, Mallinckrodt Diagnostica) 9.0–17.0 pmol/l. Patients who were examined at this time were classified as euthyroid when they had normal fT_4 and T_3 levels and were not taking thyrostatic or thyromimetic drugs. Patients with a subnormal or elevated TSH level together with normal fT_4 and T_3 levels were included in the group of euthyroid patients. The criterion for hyperthyroidism was a TSH level below 0.40 mU/l along with a fT_4 level above 17.0 pmol/l and/or a T_3 level above 3.5 nmol/l. Patients on antithyroid medication at the time of the examination were also classified as hyperthyroid. Hypothyroidism was diagnosed if the serum TSH level was above 4.00 mU/l with a serum fT_4 level below 9.0 pmol/l and in patients who were on thyromimetic therapy.

Two of the patients treated with low doses had died before February 1992: one of a cardiovascular cause and one of primary biliary cirrhosis. Seven of the patients treated with calculated doses had died: two of cardiovascular causes, one of sudden death and four of unknown causes. Three of the four patients with cardiovascular-related deaths (including one sudden death) were still hyperthyroid at the time of death.

For the nine patients who had died before February 1992, hyperthyroidism was diagnosed in those who were on antithyroid medication at the last thyroid evaluation recorded in the medical records and hypothyroidism in those who received thyroid hormone replacement at that time. For the patients not on thyrostatic or thyromimetic drugs the last biochemical analyses showed normal serum levels of thyroid hormones. Therefore, these patients were classified as euthyroid.

Life table analysis

Data from the endpoint analysis were used to determine the presence of euthyroidism (or hypothyroidism). Patients who were hyperthyroid at endpoint were classified as never having reached euthyroidism during follow-up. For euthyroid and hypothyroid patients, the last day of antithyroid drug treatment, as recorded in the medical records, was assumed to be the moment euthyroidism was achieved. For those patients who had not used antithyroid medication after the last administration of radioiodine, euthyroidism was achieved on the date 3 months after the last radioiodine therapy. For each patient, the time between the first radioiodine treatment and the moment of reaching euthyroidism was calculated. Univariate analysis of the time to reach euthyroidism, with the date of reaching euthyroidism serving as an endpoint, was performed using Kaplan-Meier survival distribution estimates. In this analysis, information from observations with incomplete follow-up (censored data) is appropriately used.

Statistical analyses

The mean values $\pm$ SEM are given. Homogeneity between groups was tested non-parametrically by means of the Wilcoxon two-sample test or the Kruskall Wallis test for multiple groups (level of significance denoted as p and p^*, respectively). For qualitative relations the chi-square test for contingency tables was used (level of significance denoted as p^{**}). Subsequent to life table analysis, the log-rank test was used to test for homogeneity across strata (level of significance denoted as p^{***}). Calculations were made using SAS statistical software [23].

4.3 Results

Radioiodine therapy

Patient characteristics and ^{131}I therapy details are provided in Table 4.1. Although almost all patients had previously used antithyroid drugs for at least 6 months, only ca. two-thirds of patients in each group were on antithyroid medication 1 week before the first radioiodine therapy. Mean thyroid weight was

higher ($p < 0.001$) in group B, treated with calculated doses, than in group A, treated with low doses, as a result of a preference to treat larger goiters with calculated doses. There were no significant differences in 3-h and 24-h RAIU between both groups ($p > 0.1$).

Table 4.1 *Patient characteristics and radioiodine therapy data* *

	Low doses (group A)	Calculated doses (group B)
Number of patients	45	58
Sex (female : male)	41 : 4	54 : 4
Age (yr) [a]	65.9 ± 1.4 (42.3–80.6)	63.3 ± 1.3 (41.2–80.1)
Time between diagnosis of hyperthyroidism and first ^{131}I therapy (yr)	5.3 ± 0.8 (0–30)	4.8 ± 0.8 (0–30)
Thyroid surgery before first ^{131}I therapy	0/45	6/58
Patients on antithyroid medication 1 wk before first ^{131}I therapy	27/45	38/58
Thyroid weight (g) [a]	73 ± 6 (31–207) (n=43)	140 ± 13 (33–395) (n=58)
3-h RAIU [a,b]	42 ± 2 (17–75) (n=45)	41 ± 2 (9–74) (n=58)
24-h RAIU [a,b]	68 ± 10 (40–83) (n=4)	61 ± 2 (37–92) (n=58)
Number of ^{131}I doses	2.2 ± 0.2 (1–7)	1.3 ± 0.1 (1–3)
Total dose (MBq)	371 ± 45 (75–1332)	903 ± 93 (96–4107)
Total dose per gram retained at 3 h (MBq/g)	2.1 ± 0.2 (0.3–7.9)	2.7 ± 0.2 (0.8–8.6)

* Values represent mean ± SEM. Numbers in parentheses are ranges

[a] Time of the first ^{131}I therapy

[b] Thyroid RAIU, measured 3 and 24 h, respectively, after oral ingestion of 0.37 MBq of ^{131}I

The number of doses of ^{131}I was significantly lower for group B ($p < 0.001$). In both groups of patients, the dose per gram retained at 3 hours was calculated for every treatment (24-h RAIU was available in only a minority of group A patients). The total dose per gram of thyroid tissue is the sum of these doses. Although the total administered dose was more than twice as high in group B as in group A ($p < 0.001$), the total dose per gram of thyroid tissue was not significantly different in both groups.

Follow-up after radioiodine therapy

Endpoint analysis

The interval between the first administration of radioiodine and the endpoint of follow-up was 4.3 ± 0.2 years (range 1.4–7.2) for group A and 5.2 ± 0.3 years (range 1.7–12.2) for group B. This difference in follow-up was not significant ($p > 0.1$). Duration from the last radioiodine treatment to the endpoint of follow-up was more than 1 year in all but three patients in group A and in all but one patient in group B. No patient had had thyroid surgery after the last radioiodine therapy.

Euthyroidism

At the end of follow-up, 30 group A patients (66%) and 47 group B patients (81%) were euthyroid. The total dose per gram of thyroid tissue did not differ significantly between the two groups of euthyroid patients (2.3 ± 0.3 MBq/g versus 2.7 ± 0.2 MBq/g; $p > 0.1$).

Persistent or Recurrent Hyperthyroidism

Twelve group A patients (27%) and seven group B patients (12%) were thyrotoxic at the end of follow-up. Of these 19 patients, 13 were on antithyroid medication and six were not treated for hyperthyroidism. Two patients, one in group A and one in group B, had received the last dose of radioiodine less than 0.5 years previously and still used antithyroid medication. The medical records revealed that seven of the other 11 patients in group A and five of the other six patients in group B had never reached euthyroidism or had become hyperthyroid again within 6 months after stopping antithyroid medication following the last radioactive iodine treatment. In these patients, persistent hyperthyroidism seems a more appropriate classification than recurrent hyperthyroidism. For varying reasons these patients were not retreated with radioactive iodine (seven patients or their treating physicians did not aim at further ^{131}I therapy, in three patients mild, persistent hyperthyroidism was not recognized and in two the reason is not known). Four patients in group A had recurrent hyperthyroidism, 0.7, 0.8,

0.9 and 1 year after stopping antithyroid medication following the last radioiodine therapy. In group B, hyperthyroidism recurred in one patient 5 years after the last radioiodine therapy.

Hypothyroidism

In group A, mild, previously undiagnosed hypothyroidism was found in one patient at the end of follow-up (TSH level 7.4 mU/l, fT_4 level 8.5 pmol/l, 3.2 years after the last therapy). Clinically, she was euthyroid. Another two patients were on L-thyroxine therapy. In one patient, L-thyroxine was started 1.9 years after the last ^{131}I treatment. Shortly before the start of replacement therapy, the serum TSH level was 29.1 mU/l. In the other patient L-thyroxine was started at a normal TSH level (0.6 mU/l) 2.1 years after the last dose of radioiodine.

In group B, two patients showed biochemical evidence of mild hypothyroidism at the end of follow-up (TSH 5.3 mU/l, fT_4 8.6 pmol/l, 6.6 years after the last therapy; TSH 8.3 mU/l, fT_4 8.0 pmol/l, 9.1 years after the last dose). Clinically, there were no signs or symptoms of hypothyroidism. Another two patients were on L-thyroxine therapy at the end of follow-up. In the first patient, the serum TSH level was 50.0 mU/l at the start of L-thyroxine therapy 1.3 years after the last dose of radioiodine. In the other, L-thyroxine had been started 0.7 years after the last dose at a TSH level of only 0.90 mU/l.

With the inclusion of two patients in whom L-thyroxine therapy was started at normal TSH levels, the overall rate of hypothyroidism was 3/45 (7%) in the group of patients treated with low doses and 4/58 (7%) in the group treated with calculated doses. Excluding these two patients, the totals are 2/44 (5%) and 3/57 (5%), respectively. More severe hypothyroidism (TSH level >10 mU/l, n = 2) was only diagnosed during the first 2 years after the last administration of radioiodine. Three of the patients with proven hypothyroidism in groups A and B were on antithyroid medication until 3 days prior to the last ^{131}I administration. TSH levels at that time were below 1.0 mU/l in two and not known in one.

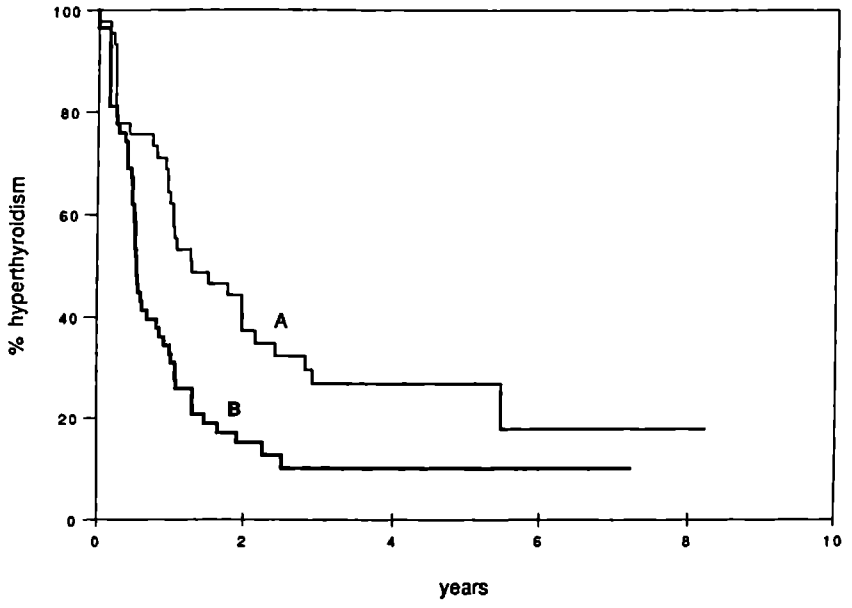
At the end of follow-up, frequencies of hypo-, eu- and hyperthyroidism did not differ significantly between groups A and B ($p^{**} = 0.163$). In group B, thyroid weight was about twice as low in the patients who became hypothyroid (79 ± 21 g) as in the ones who were hyperthyroid (158 ± 37 g) and euthyroid (140 ± 14 g) at endpoint. This difference did not, however, reach statistical significance ($p^* > 0.1$). In all 103 patients, there was no significant difference with respect to thyroid weight and administered dose per gram of thyroid tissue between patients who were hyper-, eu- and hypothyroid at the end of follow-up ($p^* > 0.1$). Furthermore, ages, sex ratios and number of therapies were similar in patients who were hyper-, hypo- or euthyroid at the end of follow-up in both group A and group B.

The number of patients who were adequately treated (*i.e.* not hyperthyroid at the end of follow-up) with a single dose was more than twice as high in group B (38/58 = 66%) as in group A (12/45 = 27%) ($p^{**} < 0.001$).

Life table analysis (Figure 4.1)

Univariate analysis of the time between the first radioiodine therapy and the achievement of euthyroidism showed that the time to reach euthyroidism was significantly shorter in patients treated with calculated doses than in patients treated with low doses (median time 0.6 years (mean ± SEM 1.0 ± 0.1 years) versus 1.5 years (mean ± SEM 2.4 ± 0.3 years; $p^{***} < 0.001$)).

Figure 4.1 *Percentage of hyperthyroid patients after treatment with low doses (A) and after treatment with calculated doses (B) plotted against time since the first radioiodine therapy (Kaplan-Meier method)*



4.4 Discussion

In two types of hyperthyroidism (toxic multinodular goiter (Plummer's disease) and toxic solitary autonomous thyroid nodule (Goetsch's disease)), the toxic thyroid nodules are supposed to secrete thyroid hormone autonomously, *i.e.* inde-

pendently of extrathyroidal stimulators. In an earlier study, we reported on results of radioiodine therapy in toxic solitary autonomous nodules [24]. In these patients, a standard dose of 740 MBq (20 mCi) of ^{131}I was highly effective, and after a mean follow-up of 10 years, the incidence of hypothyroidism was only 6%. In the present study, long-term results of two dosage schedules of radioiodine therapy are described in 103 patients with toxic multinodular goiter. The higher mean age of our patients and the clear predominance of women are in accordance with other reports in the literature on toxic multinodular goiter [25].

Remission of hyperthyroidism had been reached in 73% of the patients treated with low doses (group A) and in 88% of the patients treated with calculated doses (group B) at the end of follow-up. At that time, 27% (n = 12) and 12% (n = 7), respectively, were, still or again, thyrotoxic (13 of whom were on antithyroid medication). There was no significant difference with respect to initial thyroid weight or total administered dose of radioiodine per gram of thyroid tissue between these 19 hyperthyroid patients and the 84 patients in whom hyperthyroidism was successfully reversed. Table 4.2 shows a summary of data in the literature with respect to the percentage of patients with (multi-)nodular goiter in whom radioiodine did not result in permanent remission of hyperthyroidism. The incidence of therapy failure (persistent or recurrent hyperthyroidism) found in our study is within the range of 1%–30% reported in other studies. A comparison of these studies is difficult, however, for the reasons previously mentioned. Better results than ours with respect to reversal of hyperthyroidism were reported by Kinser *et al.* [18] and Moser *et al.* [16]. However, follow-up was short in these reports and fairly high doses were used. In contrast to these favourable results Berding and Schicha [20] reported a considerably higher incidence of hyperthyroidism after 1 year, despite the use of equally high doses.

It appears from our study that recurrent hyperthyroidism is less frequent than persistent hyperthyroidism after ^{131}I therapy for toxic multinodular goiter. Only five patients (four in group A and one in group B) had recurrent hyperthyroidism. Twelve patients (seven in group A and five in group B) had persistent hyperthyroidism. The doses we administered were not very high (50–100 Gy per treatment with a calculated dose and certainly less per treatment with a low dose). Higher doses of radioiodine may diminish the incidence of persistent hyperthyroidism [16, 18]. There is no reason to assume that remission of hyperthyroidism would not have been reached with further ^{131}I treatment in the patients with persistent hyperthyroidism: in the majority of these hyperthyroid patients radioiodine therapy was not repeated for reasons of patients' or physicians' preferences or because mild, persistent hyperthyroidism was not recognized.

Table 4.2 *Summary of data in the literature on the percentage of patients with (multi-)nodular goiter in whom radioiodine did not result in permanent remission of hyperthyroidism*

Author	Number of patients	Dose per treatment	Follow-up (yr) mean	(range)	Recurrent/ persistent hyperthyroidism
Seed [3]	55	n.m.	n.m.	(0.5–2)	31%
Eller [4] [a,b]	282	80 Gy	n.m.	(1–10)	1.4%
Lamberg [5] [b]	98	5.9 MBq/g	n.m.	(0.3–>2)	6.1%
Heinze [10]	160	60–100 Gy	n.m.	(0–14)	19%
Holm [12]	2123	100 Gy	1	(1–1)	18%
Hoeschel [13]	130	60–150 Gy	n.m.	(0.5–5.5)	6.2%
Wiener [14] [b]	88	7.4 MBq/g [c]	5.3	(1–17)	13.6%
Moser [16] [d]	118	150 Gy	0.9	(0.3–4.2)	3%
	176	400 Gy [c]	0.8	(0.3–5.7)	1%
Kinser [18]	29	300 Gy [c]	1	(1–1)	0%
Veneman [19]	48	1.5 MBq/g	9 [e]	(5–14)	33%
Berding [20]	34	150–250 Gy	1	(1–1)	24%

[a] Graves' ophthalmopathy not excluded
[b] Toxic autonomously functioning thyroid nodules not excluded
[c] per gram of hyperactive thyroid tissue
[d] Comparison of two dosage schedules
[e] Median
n.m. Not mentioned

The overall rate of hypothyroidism in our study was 7% (n = 3) in the group of patients treated with low doses and 7% (n = 4) in the group treated with calculated doses, or, excluding the two patients in whom L-thyroxine replacement therapy was started unnecessarily, 5% in each group. We could not demonstrate a significant relationship between development of hypothyroidism and initial thyroid weight or total dose per gram of thyroid tissue. In patients on antithyroid drugs, a theoretically possible cause of hypothyroidism is the irradiation of normal TSH-dependent thyroid cells when the serum TSH level is not suppressed at the time of radioiodine treatment. Three of the five patients with proven hypothyroidism were on antithyroid drugs until 3 days prior to the last radioiodine administration. In two of them, this cause for hypothyroidism could be excluded because TSH was suppressed at the time of the last radioiodine administration. In one patient the TSH level at that time is not known.

Table 4.3 *Summary of data in the literature on the incidence of hypothyroidism after therapy with radioactive iodine in patients with toxic (multi-)nodular goiter*

Author	Number of patients	Dose per treatment	Follow-up (yr) mean	Follow-up (yr) range	Hypothyroid
Seed [3]	55	n.m.	n.m.	0.5–2	3.6%
Eller [4] [a]	436	80 Gy	n.m.	1–10	7.8%
Lamberg [5] [a]	98	>5.9 MBq/g	n.m.	0.4–>2	8.2%
Dunn [6] [a]	109	7.4 MBq/g [c]	n.m.	0–15	7%
	15 [b]			>10–15	40%
Nofal [7]	145	167 Gy	n.m.	<1–16	35.9%
Viherkoski [8] [a]	313	5.2–5.9 MBq/g	n.m.	1–8	18%
Heinze [10]	160	60–100 Gy	n.m.	0–14	8.8%
Bliddal [11]	53	5.6 MBq/g	n.m.	n.m.	5.7%
Hoeschel [13]	130	60–150 Gy	n.m.	0.5–5.5	3.8%
Wiener [14] [a]	88	7.4 MBq/g [e]	5.3	1–17	1.1%
Moser [16] [d]	118	150 Gy	0.9	0.3–4.2	3%
	176	400 Gy [e]	0.8	0.3–5.7	4%
Kinser [18]	29	300 Gy [e]	9	9–9	7%
Veneman [19]	48	1.5 MBq/g	9 [f]	5–14	8.3%
Berding [20]	34	150–250 Gy	1	1–1	9%
Glanzmann [9]	722	100–120 Gy	n.m.	n.m.–10	6% [g]
Holm [12]	2123	100 Gy	n.m.	1–24	64% [g]
Jensen [15]	89	233–5550 MBq	1	0–10	16% [g]
Danaci [17]	21	555–740 mCi	n.m.	1–5	24% [g]

[a] Toxic autonomously functioning thyroid nodules not excluded
[b] Subgroup of patients with follow-up for more than 10 years
[c] Not corrected for 24-h thyroid RAIU
[d] Comparison of two dosage schedules
[e] Per gram hyperactive thyroid tissue
[f] Median
[g] Life table method
n.m. Not mentioned

In Table 4.3, a summary of data in the literature on the incidence of hypothyroidism after therapy with radioactive iodine in patients with toxic (multi-)nodular goiter is shown. The low overall incidence of hypothyroidism in our study is in accordance with most other reports with long-term follow-up in the litera-

ture [4, 6, 10, 18, 19]. A much higher overall incidence of hypothyroidism was reported by Nofal *et al.* [7], who used fairly high doses. A high incidence of hypothyroidism occurring late after radioiodine therapy for toxic multinodular goiter was reported by Holm *et al.* (based on life table analysis) [12] and Dunn *et al.* [6]. In contrast, late hypothyroidism was not found in two studies by Danaci *et al.* [17] and Glanzmann *et al.* [9] (both based on life table analysis). It seems that in our patients, late hypothyroidism was infrequent. In four of seven patients, hypothyroidism developed within 2 years of the last administration of radioiodine. In three patients (one treated with low doses and two treated with calculated doses), hypothyroidism was diagnosed for the first time at the end of follow-up, 3.2, 6.6 and 9.1 years after the last radioiodine therapy. The time of development of hypothyroidism in these patients is not exactly known. Hypothyroidism appeared to be mild in these three patients (serum TSH levels below 10 mU/l and no signs or symptoms of hypothyroidism).

Frequencies of hyper-, eu- and hypothyroidism did not differ significantly between the patients treated with low doses and those treated with calculated doses. The number of ^{131}I administrations in the patients treated with calculated doses was about half that in the patients treated with low doses and the percentage of patients who were adequately treated with a single dose was more than twice as high for the group treated with calculated doses as for the group treated with low doses (66% versus 27%). Consequently, life table analysis showed that euthyroidism was reached within a significantly shorter time after treatment with calculated doses than after treatment with low doses (median time 0.6 years versus 1.5 years).

We conclude that patients with toxic multinodular goiter can be effectively treated with radioiodine. In our experience, the long-term risk of post-treatment hypothyroidism is rather low. Euthyroidism can be reached significantly faster with doses of radioiodine calculated on the basis of thyroid weight and RAIU than by administration of low doses without increasing the risk of hypothyroidism. Since many of the patients with toxic multinodular goiter are elderly, both rapid and permanent relief of hyperthyroidism, especially in those with co-existent coronary artery disease, may be essential. Control visits in the first year after radioiodine therapy and every 1–2 years thereafter are important, as are subsequent treatments for cases of persistent thyrotoxicosis.

Acknowledgments

The authors thank Mr. Ch. Huysmans for statistical support.

4.5 References

1 Sridama V, McCormick M, Kaplan EL, Fauchet R, DeGroot LJ. Long-term follow-up study of compensated low-dose ^{131}I therapy for Graves' disease. *N Engl J Med* 1984;311:426–32

2 Goolden AWG, Stewart JSW. Long-term results from graded low dose radioactive iodine therapy for thyrotoxicosis. *Clin Endocrinol (Oxf)* 1986;24:217–22

3 Seed L, Jaffé B. Results of treatment of toxic goiter with radioactive iodine. *J Clin Endocr* 1953;13:107–19

4 Eller M, Silver S, Yohalem S, Segal R. The treatment of toxic nodular goiter with radioactive iodine: 10 years' experience with 436 cases. *Ann Intern Med* 1960; 52:976–1013

5 Lamberg B, Hernberg C, Wahlberg P, Hakkila R. Treatment of toxic nodular goitre with radioactive iodine. *Acta Med Scand* 1959;165:245–58

6 Dunn J, Chapman E. Rising incidence of hypothyroidism after radioactive-iodine therapy in thyrotoxicosis. *N Engl J Med* 1964;271:1037–42

7 Nofal M, Beierwaltes W, Patno M. Treatment of hyperthyroidism with sodium iodide I 131. *JAMA* 1966;197:605–10

8 Viherkoski M, Lamberg B, Hernberg C, Niemi E. Treatment of toxic nodular and diffuse goitre with radioactive iodine. *Acta Endocrinol (Copenh)* 1970;64:159–70

9 Glanzmann C, Kaestner F, Horst W. Therapie der Hyperthyreose mit Radio-Isotopen des Jods: Erfahrungen bei über 2000 Patienten. *Klin Wochenschr* 1975;53:669–78

10 Heinze HG, Schenk F. ^{131}J-Therapie der Hyperthyreose. *Nuklearmedizin* 1977; 16:1–12

11 Bliddal H, Hansen JM, Rogowski P, Johansen K, Friis T, Siersbaek-Nielsen K. ^{131}I treatment of diffuse and nodular toxic goitre with or without antithyroid agents. *Acta Endocrinol (Copenh)* 1982;99:517–21

12 Holm LE, Lundell G, Israelsson A, Dahlqvist I. Incidence of hypothyroidism occurring long after iodine-131 therapy for hyperthyroidism. *J Nucl Med* 1982;23:103–7

13 Hoeschel M, Heinze HG. ^{131}J-Therapie des Morbus Basedow und der nicht-immunogenen Hyperthyreose. *Nuklearmedizin* 1984;23:143–9

14 Wiener JD. Long-term follow-up after iodine-131 treatment for Plummer's disease (autonomous goitre). *Clin Nucl Med* 1985;10:256–9

15 Jensen M, Gharib H, Naessens J, Heerden van J, Mayberry E. Treatment of toxic multinodular goitre (Plummer's disease): surgery or radioiodine? *World J Surg* 1986;10:673–80

16 Moser E, Pickardt CR, Mann K, *et al.* Ergebnisse der Radiojod-Behandlung von Patienten mit immunogener und nicht-immunogener Hyperthyreose bei Anwendung unterschiedlicher Herddosen. *Nuklearmedizin* 1988;27:98–104

17 Danaci M, Feek CM, Notghi A, Merrick MV, Padfield PL, Edwards CRW. ^{131}I radioiodine therapy for hyperthyroidism in patients with Graves' disease, uninodular goitre and multinodular goitre. *NZ Med J* 1988;101:784–6

18 Kinser JA, Roesler H, Furrer T, Grütter D, Zimmermann H. Nonimmunogenic hyperthyroidism: cumulative hypothyroidism incidence after radioiodine and surgical treatment. *J Nucl Med* 1989;30:1960–5

19 Veneman TF, Weymer M, Tjabbes T, Haeften van TW. Relevance of cause of hyperthyroidism in determining its management. *Neth J Med* 1989;35:303–8

20 Berding G, Schicha H. Ergebnisse der Radiojodtherapie der manifesten Hyperthyreose und der autonomen Struma mit Euthyreose. *Nuklearmedizin* 1990;29:158–65

21 DeGroot LJ. Graves' disease diagnosis and treatment. Multinodular goiter. *In: DeGroot LJ, Stanbury JB, eds. The Thyroid and Its Diseases, 4th ed. New York: Wiley* 1975:314–67 and 637–65

22 Doering P. Gewichtsbestimmung der menschlichen Schilddrüse mit der Szintigraphie. *Klin Wochenschr* 1957;35:944

23 SAS® (Statistical Analyzing System). User's Guide: Statistics, version 5 edition. *Cary, NC 27511-8000: SAS Institute Inc.* 1985

24 Huysmans D, Corstens F, Kloppenborg P. Long-term follow-up in toxic solitary autonomous thyroid nodules treated with radioactive iodine. *J Nucl Med* 1991; 32:27–30

25 Studer H, Gerber H. Toxic multinodular goiter. *In: Braverman L, Utiger R, eds. Werner and Ingbar's The Thyroid, 6th ed. Philadelphia: Lippincott* 1991:692

Chapter

five

Significance of serum TSH levels below the normal range in patients treated with radioiodine for toxic multinodular goiter

Significance of Serum TSH levels Below the Normal Range in Patients Treated with Radioiodine for Toxic Multinodular Goiter

Huysmans DAKC, Hermus ARMM, Ross HA, Corstens FHM, Kloppenborg PWC

In a recent study (*Eur J Nucl Med* 1993; 20: 1056–62) we reported that most patients with toxic multinodular goiter after treatment with either low doses of ^{131}I (group A) or calculated doses adjusted for thyroid weight and radioactive iodide uptake (group B) were euthyroid (normal free thyroxine (fT_4) and triiodothyronine (T_3) levels and not using thyrostatic or thyromimetic drugs) at the last visit (follow-up, mean ± SD, 4.3 ± 1.3 yr for group A and 5.2 ± 2.3 yr for group B). However, it appeared that 30% of the euthyroid patients had a serum TSH level below the normal range at that time. Furthermore, significant inverse correlations between serum fT_4 and T_3 levels on one hand and serum TSH levels on the other were observed in the euthyroid patients. These observations suggest that, in spite of normal serum levels of fT_4 and T_3, autonomous thyroid function was still present in (a number of) these patients and that they are at risk of recurrent hyperthyroidism.

Forty-nine of these euthyroid patients were re-examined 1 yr later (Feb 1993). Patients of group B, rendered euthyroid after a single dose of radioiodine in the past, were also evaluated in Feb 1994 (group B select; n = 21). The follow-up data demonstrate significant decreases of serum fT_4 and T_3 levels and a significant increase in serum TSH levels after 1 yr. In the majority of patients, fT_4 levels had decreased (34 of 49 patients) or stayed at the same level (3 of 49 patients) after 1 yr. Even in 13 of 18 patients, who had a TSH value below normal in 1992, fT_4 levels had decreased 1 yr later. Significant decreases in serum fT_4 and T_3 levels were also observed between Feb 1992 and Feb 1994 in group B select. In 19 of 21 patients fT_4 levels in 1994 were lower than in 1992. On the other hand, in 12 patients of the whole group of 49 euthyroid patients and in 3 of the subgroup of 18 patients with a TSH level below normal in 1992, fT_4 levels had increased after 1 yr. An increase to fT_4 levels just above the normal range was seen in only 3 of all 49 euthyroid patients. It is concluded that in patients, treated with ^{131}I for toxic multinodular goiter in the past, who have normal fT_4 and T_3 levels, a further decrease of thyroid hormone levels can be anticipated, at least in the first decade after ^{131}I therapy. This applies even for the subgroup of patients with a serum TSH level below normal. In these patients, an expectative policy is indicated. Additional ^{131}I treatment has to be considered in patients with a serum TSH level below normal, when serial measurements show a further decrease in TSH levels in combination with increasing fT_4 and T_3 levels, especially when signs and symptoms of thyrotoxicosis recur.

5.1 Introduction

In the preceding study we reported that most patients with toxic multinodular goiter who had been treated with either low doses of radioiodine (group A) or calculated doses adjusted for thyroid weight and radioactive iodide uptake (group B) were euthyroid (defined as a normal free thyroxine (fT_4) and a normal triiodothyronine (T_3) level and not using thyrostatic or thyromimetic drugs) at the time of the last visit. However, it appeared that a considerable number of these euthyroid patients had a serum thyroid-stimulating hormone (TSH) level below the normal range at the time of the last evaluation in February 1992 (10 of 29 euthyroid patients in group A and 11 of 42 euthyroid patients in group B). The significance of the combination of a normal fT_4 and T_3 level with a TSH level below the normal range in a patient treated with radioiodine with respect to the risk of recurrent hyperthyroidism is unknown. Therefore, we reinvestigated this group of euthyroid patients one year later (February 1993). Furthermore, a subgroup of patients of group B, those who were rendered euthyroid after a single dose of radioiodine in the past, were also evaluated in February 1994.

5.2 Patients and methods

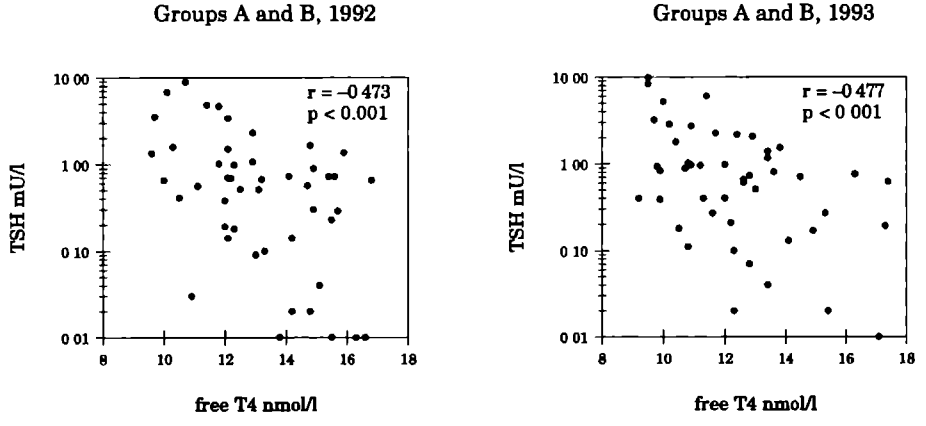
In the follow-up study in February 1993, 22 euthyroid patients of group A (20 women and 2 men, aged 69 ± 9 years, mean $\pm$ SD; range 51–85 years) and 27 euthyroid patients of group B (25 women and 2 men, aged 66 ± 9 years; range 46–82 years) were included. In February 1992, the time since the last dose of radioiodine was 3.8 ± 1.4 years for the 22 patients of group A and 5.2 ± 2.8 years for the 27 patients of group B. Reasons why patients were not included in the follow-up study in February 1993 were death in the preceding year (n = 2), refusal of the patient to cooperate (n = 1) and impossibility to analyze samples obtained in 1992 and 1993 of the same person in one assay run due to shortage of serum obtained in 1992 (n = 19). Twenty-one of 32 patients of group B (19 women and 2 men, aged 68 ± 8 years; range 48–82 years), who were euthyroid in 1992 after a single dose of radioiodine in the past, were included in the study in February 1994 (group B select; follow-up in 1992 5.5 ± 3.0 years). Evaluation consisted of a short medical interview and blood sampling for measurement of serum levels of TSH, T_3, T_4 and fT_4 (for assays and normal ranges see Chapter 4).

Statistical analyses were performed using the Wilcoxon sign-rank test for paired observations (p-values denoted as p) and the Spearman rank-correlation test (p-values denoted as p^*). The mean values $\pm$ SD are given.

5.3 Results

In February 1992, significant inverse correlations were present between serum levels of fT_4 and TSH ($r = -0.409$, $p^* < 0.001$) and between serum levels of T_3 and TSH ($r = -0.320$, $p^* < 0.01$) in the total group of 71 euthyroid patients of groups A (n = 29) and B (n = 42). When the data of the 49 patients of groups A and B who participated in the follow-up study in February 1993 were combined, a significant inverse correlation between serum levels of fT_4 and TSH was present both in February 1992 ($r = -0.473$, $p^* < 0.001$; Figure 5.1, left panel) and in February 1993 ($r = -0.477$, $p^* < 0.001$; Figure 5.1, right panel). In this group of 49 patients the inverse correlation between serum levels of T_3 and TSH was significant in 1992 ($r = -0.363$, $p^* < 0.02$) but not significant in 1993 ($r = -0.151$, $p^* > 0.1$). No significant correlations could be demonstrated between serum levels of TSH, T_3, T_4 or fT_4 on one hand and the time since the last radioiodine therapy on the other, neither for groups A and B separately, nor when the data for both groups were combined.

Figure 5.1 *Serum TSH levels (on a logarithmic scale) of 49 patients of groups A and B combined, plotted against serum fT_4 levels in February 1992 (left panel) and February 1993 (right panel)*



Changes in thyroid function during 1 year follow-up (groups A and B)
Table 5.1 shows levels of TSH, T_3, T_4 and fT_4 as measured in serum samples obtained in 1992 and 1993. No antithyroid or thyromimetic medication was started between February 1992 and February 1993 in any patient of groups A and B. In

both groups, TSH levels increased and T_3, T_4 and fT_4 levels decreased, changes being statistically significant for T_3 in group A, for TSH and T_4 in group B and for fT_4 in both groups. When groups A and B were combined, changes in all hormone levels were highly significant ($p < 0.01$).

Table 5.1 *Serum levels (mean ± SD) of TSH, T_3, T_4 and fT_4, in February 1992 and February 1993 in patients in group A, group B and groups A and B combined*

		TSH	T_3	T_4	fT_4
Group A	1992	1.16 ± 2.05	2.0 ± 0.4	104 ± 17	13.0 ± 1.9
(n=22)	1993	1.34 ± 2.27	1.7 ± 0.3	101 ± 15	12.0 ± 2.1
	p	ns	<0.006	ns	<0.002
Group B	1992	1.30 ± 1.66	1.8 ± 0.3	106 ± 20	12.9 ± 2.5
(n=27)	1993	1.51 ± 1.89	1.7 ± 0.3	102 ± 17	12.3 ± 2.5
	p	<0.04	ns	<0.03	<0.04
Groups A and B	1992	1.24 ± 1.82	1.9 ± 0.4	105 ± 19	13.0 ± 2.2
(n=49)	1993	1.43 ± 2.05	1.7 ± 0.3	101 ± 16	12.2 ± 2.3
	p	<0.008	<0.001	<0.004	<0.001

Figure 5.2 *Serum free T_4 levels in February 1992 and February 1993 plotted against the time since the last radioiodine therapy, for group A (left panel) and group B (right panel)*

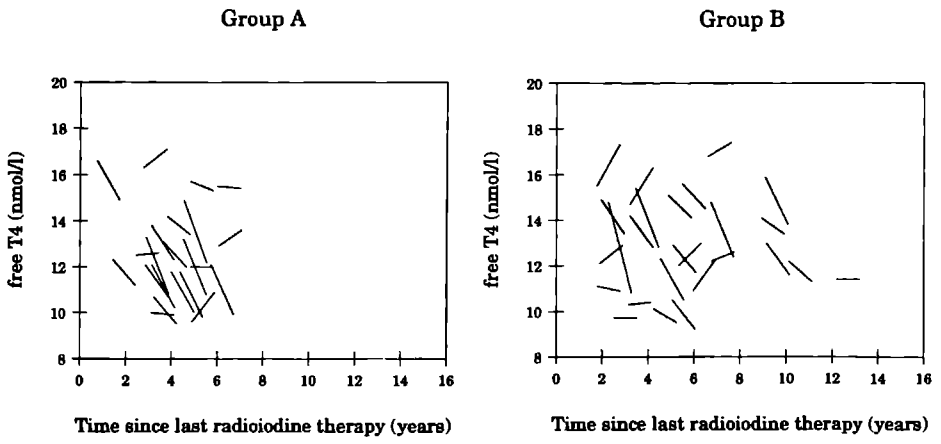


Figure 5.2 shows fT_4 levels in 1992 and 1993 for the individual patients in groups A (Figure 5.2, left panel) and B (Figure 5.2, right panel) plotted against the time since the last radioiodine therapy. In the majority of patients, fT_4 levels decreased (17 patients of each group) or stayed at the same level (1 patient of group A and 2 of group B). In only 12 patients (4 of group A and 8 of group B) fT_4 levels increased, which was accompanied by a decrease in the serum TSH level in 5 patients while in one patient the serum TSH level stayed undetectable. For patients who had been treated with radioiodine more than 5 years ago, fT_4 levels decreased in 5 of 8 patients in group A and in 10 of 15 patients of group B.

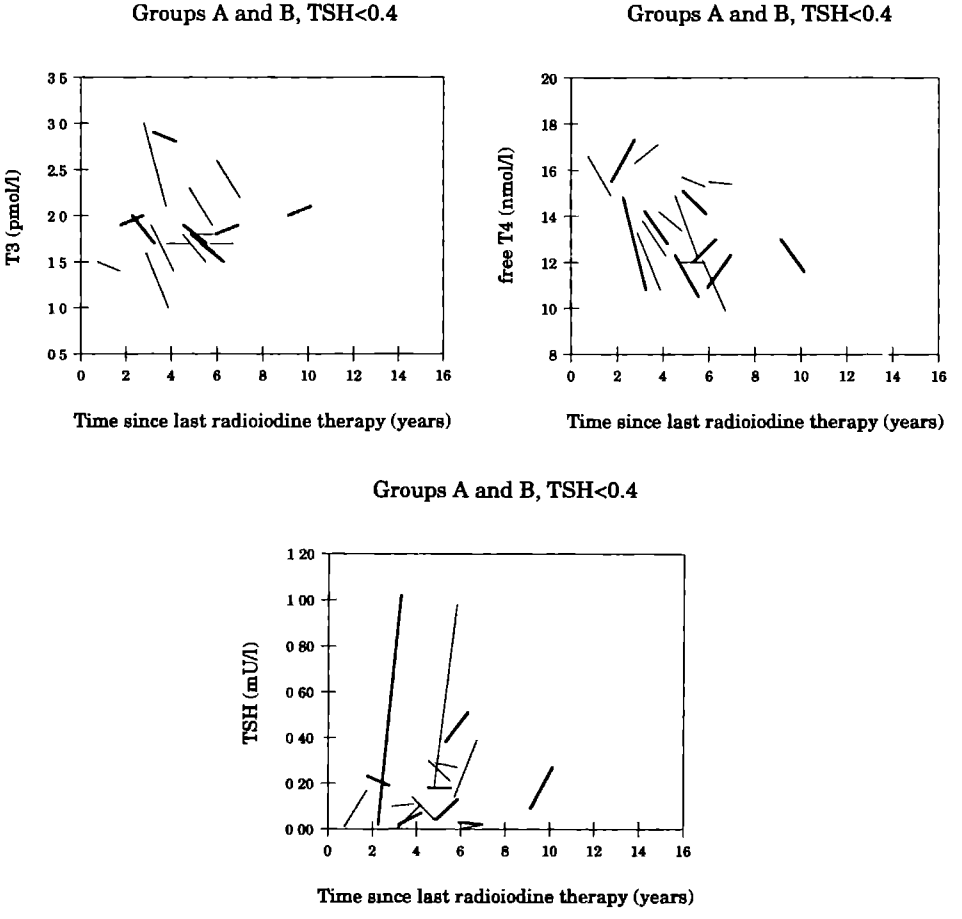
Table 5.2 *Serum levels (mean ± SD) of TSH, T_3, T_4 and fT_4 in February 1992 and February 1993 in patients of group A, group B and groups A and B combined, who had a serum TSH level below the normal range in 1992*

		TSH	T_3	T_4	fT_4
Group A	1992	0.12 ± 0.12	2.0 ± 0.5	105 ± 21	14.4 ± 1.6
TSH<0.4 in 1992	1993	0.23 ± 0.29	1.7 ± 0.4	100 ± 18	13.3 ± 2.3
(n=10)	p	ns	<0.02	ns	<0.02
Group B	1992	0.12 ± 0.13	2.0 ± 0.4	111 ± 21	13.5 ± 1.7
TSH<0.4 in 1992	1993	0.30 ± 0.33	1.9 ± 0.4	108 ± 17	12.8 ± 2.2
(n=8)	p	<0.05	ns	ns	ns
Groups A and B	1992	0.12 ± 0.12	2.0 ± 0.4	108 ± 21	14.0 ± 1.7
TSH<0.4 in 1992	1993	0.26 ± 0.30	1.8 ± 0.4	103 ± 18	13.1 ± 2.2
(n=18)	p	<0.04	<0 01	<0.05	<0.03

Changes in thyroid function in the subgroup of patients, who had a serum TSH level below normal (<0.4 mU/l) in 1992 were similar to those of the whole group (Table 5.2). When data from patients of groups A and B were combined, a significant increase in the serum TSH level as well as significant decreases in serum levels of T_3, T_4 and fT_4 were observed. In Figure 5.3, serum levels of T_3, fT_4 and TSH in the individual patients of the combined subgroups in 1992 and 1993 are plotted against the time since the last radioiodine therapy. Only 4 patients had an increasing fT_4 level; in 13 patients fT_4 decreased from 1992 to 1993 and in one patient it stayed at the same level. In 3 of the 4 patients with an increasing fT_4 level the serum TSH level decreased or stayed undetectable. A decreasing or constant fT_4 level was accompanied by an increasing TSH level

in 11 of 14 patients and by a decreasing T_3 level in 9 of 14 patients. For 3 of the 18 patients with a TSH level below normal in 1992, a normal TSH value was found in 1993, whereas none of the patients with a normal TSH level in 1992 had a TSH level below the normal range in the next year.

Figure 5.3 *Serum T_3 (upper left panel), free T_4 (upper right panel) and TSH levels (lower panel), in February 1992 and February 1993 in patients with a serum TSH level below the normal range in 1992, plotted against the time since the last radioiodine therapy. Patients of group A are indicated by bold lines and patients of group B by hairlines*



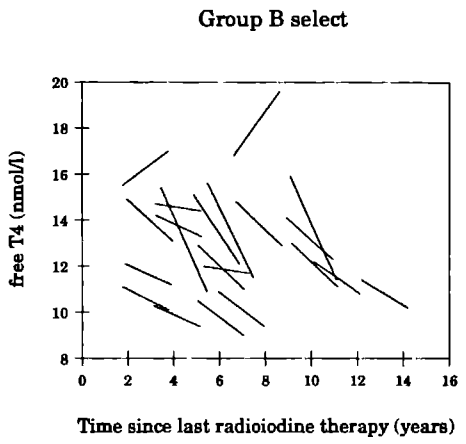
In 1993, marginally elevated fT_4 levels were found in one patient of group A (TSH < 0.01 mU/l and fT_4 16.3 pmol/l in 1992; TSH < 0.01 mU/l and fT_4 17.1 pmol/l in 1993) and in two patients of group B (TSH 0.23 mU/l and fT_4 15.5 pmol/l in 1992 and TSH 0.19 mU/l and fT_4 17.3 pmol/l in 1993 for one patient; TSH 0.65 mU/l and fT_4 16.8 pmol/l in 1992 and TSH 0.62 mU/l and fT_4 17.4 pmol/l in 1993 for the other). In none of the patients of groups A and B hypothyroidism (TSH level elevated and fT_4 level below normal) developed during the year of follow-up.

Changes in thyroid function during 2 years follow-up (group B select)
Table 5.3 (upper panel) shows levels of TSH, T_3, T_4 and fT_4 for group B select in serum samples of 1992 and 1994. Significant decreases in serum levels of T_3, T_4 and fT_4 were found, although the increase of the TSH level was not significant. The same data for the 6 patients of group B select who had a serum TSH level below the normal range in 1992 are shown in the lower panel of Table 5.3. In 19 of 21 patients fT_4 levels in 1994 were lower than in 1992 (Figure 5.4). Notably, in the two patients with a rising fT_4 level, fT_4 levels in 1992 were the highest of all patients of group B select.

Table 5.3 *Serum levels (mean ± SD) of TSH, T_3, T_4 and fT_4 in February 1992 and February 1993 in patients of group B, who had been rendered euthyroid by a single, calculated dose of radioiodine in the past (group B select; upper panel) and from the subgroup of these patients who had a serum TSH level below the normal range in 1992 (group B select, TSH < 0.4; lower panel)*

		TSH	T_3	T_4	fT_4
Group B select	1992	0.95 ± 1.07	1.8 ± 0.4	108 ± 18	13.5 ± 2.0
(n=21)	1994	0.98 ± 1.00	1.7 ± 0.3	99 ± 14	12.0 ± 2.5
	p	ns	<0.03	<0.003	<0.002
Group B select	1992	0.13 ± 0.14	2.0 ± 0.4	109 ± 22	13.5 ± 1.8
TSH<0.4	1994	0.25 ± 0.18	1.8 ± 0.4	100 ± 21	12.4 ± 2.6
(n=6)	p	<0.04	<0.04	ns	ns

Figure 5.4 *Serum free T_4 levels in February 1992 and February 1994 in patients of group B select, plotted against the time since the last radioiodine therapy*



5.4 Discussion

Significant inverse correlations between serum fT_4 and T_3 levels on one hand and serum TSH levels on the other were observed in a group of 71 patients, who were euthyroid in February 1992, 1 to 12 years after radioiodine treatment for toxic multinodular goiter. This is in contrast to the normal population in which fT_4 and TSH serum levels are independent parameters [1]. Furthermore, 21 (30%) of these patients had a serum TSH level below the normal range at that time. These observations suggest that autonomous thyroid function was still present in this group of radioiodine treated patients, notwithstanding normal serum levels of fT_4 and T_3. The question then arises, whether the administered dose of radioiodine in these patients has sufficiently destroyed the autonomously functioning thyroid tissue. Therefore, we followed changes in thyroid function during 1 or 2 years of follow-up in these patients.

Our follow-up data in 49 patients demonstrated significant decreases of serum fT_4 and T_3 levels and a significant increase in serum TSH levels after 1 year. In the majority of patients, fT_4 levels had decreased (34 of 49 patients) or stayed at the same level (3 of 49 patients). Even in 13 of 18 patients, who had a TSH value below the normal range and normal fT_4 and T_3 levels in 1992, fT_4 levels had decreased 1 year later. Furthermore, after 2 years, significant

decreases in serum fT_4 and T_3 levels were observed in the group of 21 patients, who had been rendered euthyroid by a single, calculated dose of radioiodine in the past. In 19 of these patients fT_4 levels in 1994 were lower than in 1992. We speculate that the decrease in thyroid hormone levels as observed in the majority of patients in this study is a late consequence of radioiodine treatment [2]. Our findings are similar to those of Davies *et al.*[3]. In the latter study, however, no distinction was made between patients with Graves' disease, toxic multinodular goiter or toxic solitary autonomous nodules.

On the other hand, in six of the whole group of 49 euthyroid patients and in three of the subgroup of 18 patients with a TSH level below normal in 1992, fT_4 levels had increased and serum TSH levels had decreased after 1 year. However, in only three of all 49 euthyroid patients an increase of fT_4 levels to (marginally) elevated values was seen. Further follow-up will learn whether radioiodine treatment has insufficiently destroyed the autonomously functioning thyroid tissue in these patients.

We conclude that in patients, who have been treated with radioiodine for toxic multinodular goiter in the past and who have fT_4 and T_3 levels within the normal range, a further decrease of thyroid hormone levels can be anticipated, at least in the first decade after radioiodine therapy. This applies also for the subgroup of patients with serum TSH levels below the normal range. Therefore, in patients who show the combination of normal T_3 and fT_4 levels and a TSH level below normal after radioiodine treatment for toxic multinodular goiter in the past, yearly control visits with an expectative policy is indicated. Additional ^{131}I treatment has to be considered in patients with a serum TSH level below the normal range, when serial measurements show a further decrease in TSH levels (or TSH levels below the detection limit of the assay) in combination with increasing fT_4 and T_3 levels, especially when signs and symptoms of thyrotoxicosis recur.

5.5 References

1 Meier CA, Maisey MN, Lowry A, Müller J, Smith MA. Interindividual differences in the pituitary-thyroid axis influence the interpretation of thyroid function tests. *Clin Endocrinol* 1993;39:101–7

2 Malone JF, Cullen MJ. Two mechanisms for hypothyroidism after ^{131}I therapy. *Lancet* 1976;ii:73–5

3 Davies PH, Franklyn JA, Daykin J, Sheppard MC. The significance of TSH values measured in a sensitive assay in the follow-up of hyperthyroid patients treated with radioiodine. *J Clin Endocrinol Metab* 1992;74:1189–94

Chapter

six

Magnetic resonance imaging for volume estimation of large multinodular goiters; a comparison with scintigraphy

Published as:

Magnetic Resonance Imaging for Volume Estimation of Large Multinodular Goitres; A Comparison with Scintigraphy

Huysmans DAKC, De Haas MM, Van den Broek WJM,
Hermus ARMM, Barentsz JO, Corstens FHM, Ruijs SHJ

British Journal of Radiology 1994;67:519–23

As a result of increasing interest in non-surgical treatment for the reduction of goiter size the use of magnetic resonance (MR) imaging for volume estimation of large multinodular goiters was evaluated in 20 patients (three males and 17 females; age 61 ± 21 years) with a multinodular goiter larger than 100 ml. In addition, MR measurements were compared with scintigraphic (SC) volume estimations. Intraobserver coefficient of variation (CV) of MR measurements was 2.2% ± 2.0% (Observer 1) and interobserver CV 4.1% ± 2.2% (Observers 1 and 2). In all 20 patients signs of mechanical complications were shown on MR images. For SC measurements intraobserver CV was 7.5% ± 5.7% (Observer 3) and 5.4% ± 5.1% (Observer 4). Interobserver CV was 10.1% ± 6.1%. The correlation between measurements with both methods was not strong (r = 0.665) and the resulting CV was 17.3% ± 14.2%. Underestimation of SC volumes could not be explained by the presence of cysts at the surface of the thyroid. It is concluded that MR imaging can be used for *in vivo* thyroid volume estimation in large multinodular goiters. The high precision of MR measurements makes this technique potentially useful for the evaluation of thyroid growth and non-surgical treatment for reducing goiter size. Scintigraphic volume measurements do not suffice for this purpose. An additional advantage of MR imaging is the detailed anatomical information it provides with regard to mechanical complications of large goiters.

6.1 Introduction

In recent years interest in non-surgical treatment of goiters (administration of thyroid hormone or radioiodine) has grown. Precise measurements of gland volume are necessary for the evaluation of the effects of thyroid volume reducing therapy.

Palpation is an imprecise method in the estimation of thyroid size [1, 2], as it is influenced by the neck architecture and by the experience of the observer. In the 1950s, thyroid scintigraphy was introduced to estimate thyroid volume. For diffuse goiters this method proved to be more accurate than palpation and has been used widely [3–10]. More recently, the use of ultrasound for thyroid volume estimations has been extensively studied, again chiefly in normal thyroids and diffuse goiters [10–18]. Ultrasound provides more accurate volume measurements than scintigraphy for diffuse thyroid glands [11, 12, 14, 15] and probably also for smaller multinodular goiters [19].

For large multinodular goiters, however, ultrasound becomes less reliable because of frequent intrathoracic extension [20, 21]. Despite obvious advantages of magnetic resonance (MR) imaging over ultrasound and computed tomography, such as a high soft tissue contrast, multiplanar imaging capabilities, absence of ionizing radiation and superior anatomic detail, its application for volume estimations of goiters has thus far not been reported. The purpose of the present study is to evaluate the use of MR imaging in volume estimation of large multinodular goiters. These measurements were compared with scintigraphic (SC) volume estimations in order to determine if the precision of a simple technique like planar scintigraphy is sufficient for the evaluation of the effects of thyroid volume reducing treatment in patients with large multinodular goiters.

6.2 Patients and methods

Twenty patients (three males and 17 females) were studied (age 61 ± 21 years; mean $\pm$ SD). Sixteen patients were euthyroid and four hyperthyroid. All patients had a large multinodular goiter which was estimated by palpation to be larger than 100 ml.

MR imaging

MR imaging was performed on a whole-body MR scanner (Siemens H15, Siemens AG, Erlangen, FRG), operating at a field strength of 1.5 Tesla. T_1-weighted images (TR = 270 ms, TE = 15 ms; matrix 128×256, 7 acquisitions) were obtained using a Helmholz neck coil and covering the entire goiter in the coronal, sagittal and axial planes. The slice thickness was 8 mm with a 0.8 mm slice gap. T_2-weighted images (TR = 1710 ms, TE = 80 ms) were obtained in the axial plane.

The thyroid outline was drawn manually on each slice of the T_1-weighted images. A computer program was used to calculate the surface of the traced areas. The sum of the traced surfaces in each plane was multiplied by the slice distance (0.88 cm) in order to calculate the thyroid volume.

MR measurements in the coronal plane were performed by two independent observers (Observers 1 and 2). Observer 1 repeated the measurement in the coronal plane after an interval of at least 1 month and, in addition, measured thyroid volumes in the sagittal and axial plane.

Scintigraphy

Rectilinear scintigrams were obtained 24 hours after oral ingestion of 7.5–11.1 MBq of iodine-131, using a Magna Scanner 1000 (Picker, Illinois, USA) with a 5 inch crystal probe and a high energy collimator, 5 inch focus, 0.5 inch resolution. Each of two other independent observers (Observers 3 and 4) evaluated the real size (1 : 1) images of the thyroid and again after an interval of 2 months. The traced surface on the scan was measured planimetrically and thyroid volume was calculated using the formula of Doering [6]: thyroid volume (ml) = $0.326 \times (\text{planimetric surface})^{3/2}$.

Statistical analyses

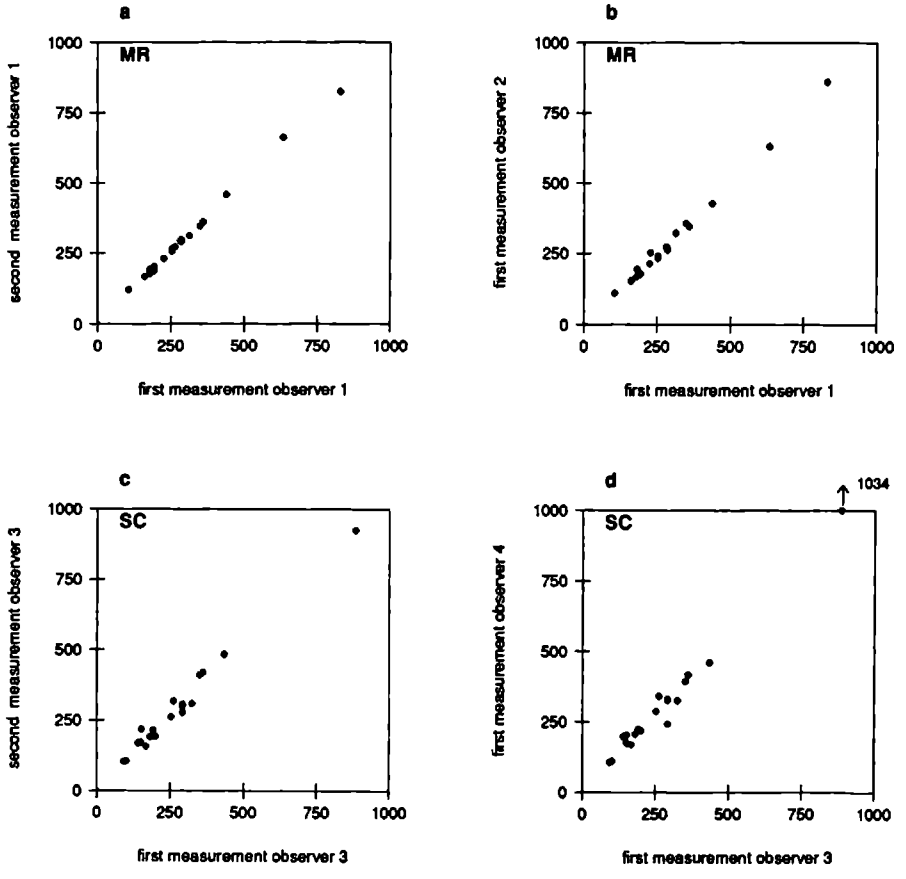
Mean values $\pm$ SD are given. Intraobserver variability and interobserver variability of MR and SC measurements and differences between MR and SC volume measurements were determined by calculating the mean coefficient of variation (CV). Correlations between two series of measurements were tested using Spearman's rank correlation test (r); level of significance denoted as p.

6.3 Results

MR imaging

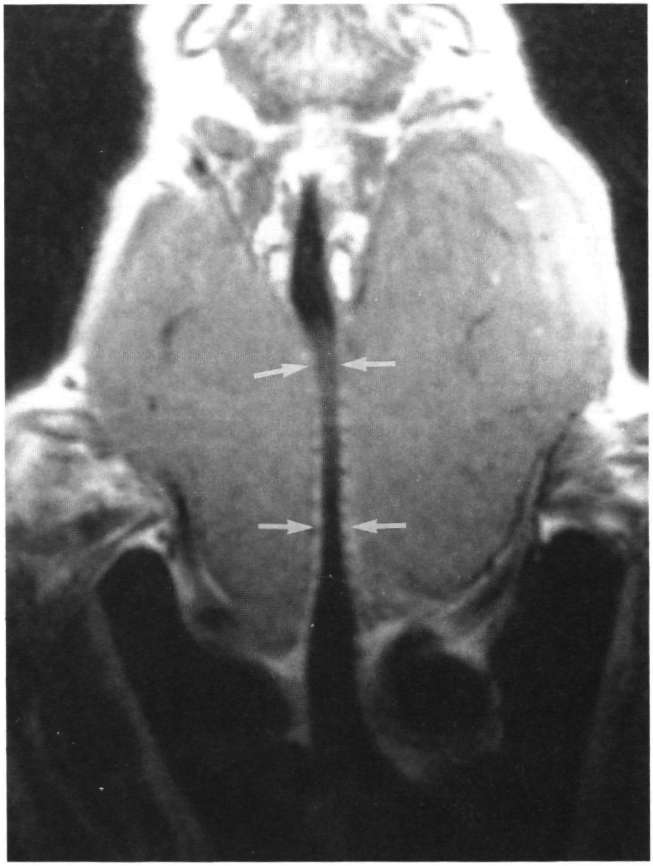
Figure 6.1a shows excellent reproducibility of the first and second measurements in the coronal plane by Observer 1. Intraobserver CV was only 2.2% ± 2.0% (Spearman's rank correlation r = 0.994, p < 0.001).

Figure 6.1 *Results of thyroid volume measurements (in ml) with MR imaging (a and b) and scintigraphy (c and d): a. first versus second measurement of Observer 1 in coronal MR images, b. first measurement of Observer 1 versus measurement of Observer 2 in coronal MR images, c. first versus second measurement Observer 3 in scintigraphic images, d. first measurement of Observer 3 versus first measurement of Observer 4 in scintigraphic images*



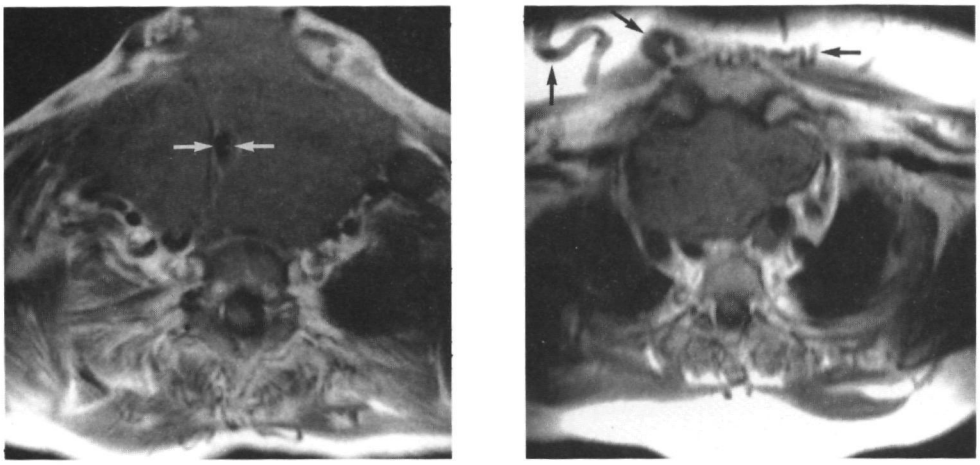
Interobserver CV for the coronal measurements of Observer 1 (first measurement) and 2 was also low: $4.1\% \pm 2.2\%$ ($r = 0.985$, $p < 0.001$; Figure 6.1b). Measurements by Observer 1 in the three imaging planes correlated very well. CVs were as follows: coronal/sagittal $3.1\% \pm 2.3\%$ ($r = 0.981$, $p < 0.001$), coronal/axial $2.3\% \pm 1.8\%$ ($r = 0.993$, $p < 0.001$) and sagittal/axial $3.2\% \pm 2.6\%$ ($r = 0.983$, $p < 0.001$).

Figure 6.2 *(a) Coronal and (b) axial T_1-weighted (TR = 270 ms, TE = 15 ms) MR images showing bilateral tracheal compression (arrows). (c) MR image in another patient showing intrathoracic goiter and collateral veins (arrows)*



A

Figure 6.2 *Continued*



B C

Intrathoracic extension of the thyroid of more than 2 cm was present in 18 patients. In all 20 patients signs of mechanical compression were found: tracheal deviation in 19, tracheal compression in 17 and distended neck veins and/or collateral vessels in six. An example is shown in Figure 6.2. T_2-weighted images showed cysts of more than 2 cm in diameter in 11 patients. Cysts localized at the periphery of the thyroid were present in seven patients.

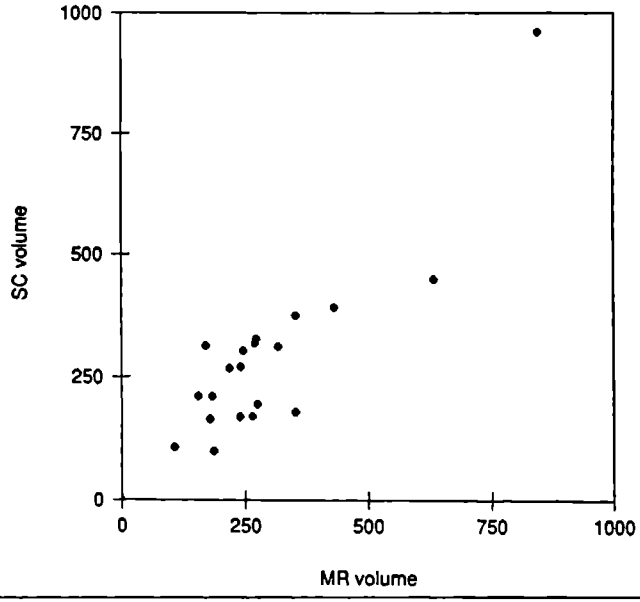
Scintigraphy

Figure 6.1c shows the results of the two measurements by Observer 3 and Figure 6.1d the results of the first measurements of Observers 3 and 4. Intraobserver and interobserver variability for scintigraphic measurements were higher than for MR measurements. Intraobserver CV was $7.5\% \pm 5.7\%$ for Observer 3 and $5.4\% \pm 5.1\%$ for Observer 4 ($r = 0.939$, $p < 0.001$ and $r = 0.973$, $p < 0.001$, respectively). Interobserver variability (first measurements) was considerable: CV $10.1\% \pm 6.1\%$ ($r = 0.941$, $p < 0.001$).

Comparison of MR imaging and scintigraphy

For each patient the mean of the MR coronal measurements of Observers 1 (first measurement) and 2 was compared with the mean of the first SC measurements of Observers 3 and 4. The results are shown in Figure 6.3. Although statistically significant ($p = 0.0038$), the correlation between measurements with

Figure 6.3 *Results of thyroid volume measurements (in ml) with MR imaging (mean of first measurements in the coronal plane of Observers 1 and 2) and scintigraphy (mean of first scintigraphic measurements of Observers 3 and 4)*



both methods was not strong (r = 0.665) and the resulting CV was as high as 17.3% ± 14.2% .

SC volume differed 0%–10% from MR volume in five patients, 11%–20% in five, 21%–30% in five, 31%–40% in two and more than 40% in three patients. In one patient the difference between measurements with both techniques was 80%. In 10 patients SC volume was larger than MR volume, in the other 10 patients SC volume was smaller than MR volume.

Cysts (without radioiodine uptake) in central parts of the thyroid are not likely to have influenced SC volume measurements. Cysts at the thyroid surface, however, may have caused an underestimation of SC volume: four of the patients in whom SC volume was smaller than MR volume had peripheral cysts on MR images. The cysts, however, were not large enough to offer a full explanation of the difference between SC and MR volume in these four patients (range of difference 96–185 ml). In three other patients with peripheral cysts SC volume was larger than MR volume.

6.4 Discussion

Two types of thyroid volume can be distinguished: the functional and the anatomical volume. The functional volume, *i.e.* the volume of the hormone secreting thyroid tissue, is of importance for dosage calculations prior to radioiodine therapy. For evaluation of thyroid growth and of non-surgical treatment of goiters, however, the anatomical volume is essential.

Thyroid volumes have been calculated scintigraphically [3–7, 9, 10, 22] with the use of formulæ incorporating one or more of the following parameters: planimetrically determined thyroid surface on the scintigram, directly measured height and width and indirectly estimated thickness of the thyroid lobes. The scintigraphic technique has proved to be more accurate than palpation [3, 6, 8]. However, results vary considerably between studies [3, 4, 7, 9, 10]. Comparing scintigraphic measurements with postoperatively and *post mortem* measured volumes, Allen and Goodwin [3] found a mean difference of 10.6% (maximum difference 25%) and Fazakas *et al.* [7] reported a mean difference of 18% (maximum difference 30%). Compared with surgical specimens, Brown and Spencer [10] found a mean underestimation of 20% by scintigraphic measurements and the maximum difference between both methods was as large as 236%.

The introduction of ultrasound has improved anatomical thyroid volume measurement. Highly significant correlations with both surgical and *post mortem* specimens have been reported by several authors [11, 14–16, 19]. Comparing ultrasound measurements with *post mortem* specimens, Von Gutjahr *et al.* [15] found a maximum difference of only 9%. Brunn *et al.* [13] reported higher mean and maximum differences compared to *post mortem* specimens (16% and 35%, respectively). In a comparison of ultrasound measurements with surgical specimens, Azagra *et al.* [18] found a mean difference of 26% (maximum 63%).

The above mentioned studies on thyroid measurements using scintigraphy or ultrasound have been carried out in patients with a normal thyroid, a diffusely enlarged gland or, in some cases, a solitary thyroid nodule. Most of the formulæ used for the calculation of thyroid volumes are based on the assumption that the thyroid lobes are ovoid. This assumption is valid for most normal and diffusely enlarged thyroid glands. However, in multinodular goiters thyroid shape is often distorted by the presence of nodules of varying size. It can, therefore, be assumed that the accuracy of both techniques will be lower in multinodular goiters. Ultrasound is probably sufficient for smaller multinodular glands if planimetry of serial slices is used instead of a formula based on an ovoid shape of the thyroid lobes [19]. However, as sternum and clavicles present anatomic

limitations for ultrasound measurements, this technique cannot be used for the measurement of large multinodular goiters, because of intrathoracic extension in most of these cases.

In this study, MR imaging (T_1-weighted sequences) was used for the measurement of the anatomical volume of large multinodular goiters. MR measurements showed a very high precision (*i.e.* the degree to which repeated computations are reproducible). Intraobserver and interobserver variability were very small (CV 2% and 4%, respectively) and the correlations between measurements in the three imaging planes were excellent. Scintigraphic estimations showed considerably larger intraobserver and interobserver variability than MR estimations (CV 7% and 10%, respectively). Although scintigraphic volume estimations were significantly correlated with MR measurements, important differences were found in a considerable number of patients and comparison of the two methods showed a CV as large as 17%.

There is no valid gold standard for volume measurements of large goiters. The volume of the surgical specimen does not represent the true thyroid volume because of manipulation, squeezing and bleeding during operation. Furthermore, (near-)complete removal of large goiters is virtually impossible (and visual estimation of the volume of the retained tissue adds to the inaccuracy). Thus, because surgical, and even *post mortem*, specimens [12] cannot be regarded as a true gold standard, it is impossible to determine the accuracy of MR measurements (*i.e.* the closeness of the computations to the true values) in patients with a large multinodular goiter. However, as MR measurements showed a very good reproducibility, this technique should be reliable in the evaluation of thyroid growth and the assessment of non-surgical treatment of goiters.

It is concluded that MR imaging can be used for *in vivo* thyroid volume estimation in large multinodular goiters. The high precision of MR measurements makes this technique potentially useful for the evaluation of thyroid growth and impact of non-surgical therapy of goiters. Scintigraphic volume measurements do not suffice for this purpose. An additional advantage of MR imaging is the detailed anatomical information it provides with regard to mechanical complications of large goiters.

6.5 References

1 MacLennan R, Gaitan E, Miller MC. Observer variation in grading and measuring the thyroid in epidemiological surveys. *In: Stanbury JB, ed. Endemic Goitre. Pan American Health Organisation: Scientific Publication 193* 1969:66–77

2 Daniels GH. Physical examination of the thyroid gland. *In: Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid, 6th ed. Philadelphia: Lippincott* 1991:572–7

3 Allen HC, Goodwin WE. The scintillation counter as an instrument for *in vivo* determination of thyroid weight. *Radiology* 1952;58:68–79

4 Goodwin WE, Cassen B, Bauer FK. Thyroid gland weight determination from thyroid scintigrams with postmortem verification. *Radiology* 1953;61:88–92

5 Himanka E, Larsson LG. Estimation of thyroid volume. *Acta Radiol* 1955;43:125–31

6 Doering P, Kramer K. Die Bestimmung des Schilddrüsengewichtes mit der Szintigraphie nach Gabe von Radiojod; Ein Beitrag zur Dosierung des Radioisotopes. *Strahlenther* 1958;105:245–59

7 Fazakas S, Balázs Gy, Petrányi Gy, Szeleczky Gy. Zur Bestimmung des Schilddrüsengewichtes mittels einer szintigraphischen Methode. *Nuklearedizin* 1964; 4:56-62

8 Malamos B, Vagenakis AG, Pandos PG, *et al.* Comparison of scanning and palpation in the assessment of the weight of the thyroid gland. *Endokrinologie* 1970;56:232–40

9 Mandart G, Erbsmann F. Estimation of thyroid weight by scintigraphy. *Int J Nucl Med Biol* 1975;2:185–8

10 Brown MC, Spencer R. Thyroid gland volume estimated by use of ultrasound in addition to scintigraphy. *Acta Radiol Oncol* 1978;17:337–41

11 Hülse R, Hahn K, Wolf R. Die Bestimmung des Schilddrüsengewichtes mit Hilfe von Szintigraphie und Ultraschall-Tomographie. *Strahlenther* 1972;72:454–7

12 Rasmussen SN, Hjorth L. Determination of thyroid volume by ultrasonic scanning. *J Clin Ultrasound* 1974;2:143–7

13 Brunn J, Block U, Ruf G, *et al.* Volumetrie der Schilddrüsenlappen mittels Realtime-Sonographie. *Dtsch Med Wochenschr* 1981;106:1338–40

14 Hegedüs L, Perrild H, Poulsen LR, *et al.* The determination of thyroid volume by ultrasound and its relationship to body weight, age, and sex in normal subjects. *J Clin Endocrinol Metab* 1983;56:260–3

15 Von Gutjahr G, Störkel S, Kraus W, *et al.* Sonographie der Schilddrüse: Volumenbestimmung und morphologische Korrelation von Echo- und Gewebestruktur. *Fortschr Röntgenstr* 1984;141:297–303

16 Yokoyama N, Nagayama Y, Kakezono F, *et al.* Determination of the volume of the thyroid gland by a high resolutional ultrasonic scanner. *J Nucl Med* 1986; 27:1475–9

17 Nagayama Y, Ashizawa K, Matsuo K, *et al.* Radioiodine (^{131}I) therapy of Graves' disease: use of the new high resolutional ultrasonic scanner for the determination of the accurate weight of the thyroid gland. *Endocrinol Japon* 1989;36:359–65

18 Azagra JS, Frédéric N, Demeester-Mirkine N, *et al.* Valeur de l'échographie pour la mesure des volumes de la glande thyroïde et de ses lésions. *J Radiol* 1990; 71:109–11

19 Berghout A, Wiersinga WM, Smits NJ, Touber JL. Determinants of thyroid volume as measured by ultrasonography in healthy adults in a non-iodine deficient area. *Clin Endocrinol (Oxf)* 1987;26:273–80

20 Berghout A, Wiersinga WM, Smits NJ, Touber JL. The value of thyroid volume measured by ultrasonography in the diagnosis of goitre. *Clin Endocrinol (Oxf)* 1988;28:409–14

21 Hegedüs L. Thyroid size determined by ultrasound. *Dan Med Bull* 1990;37:249–63

22 Hoppe G, Meüsel P. Vergleichende Untersuchungen zur Gewichtsbestimmung der Schilddrüse aus dem Scannerbild. *Fortschr Geb Röntgenstr Nuklearmed* 1965; 103:81–90

Chapter

seven

Large, compressive goiters
treated with radioiodine

Published as:

Large, Compressive Goiters Treated with Radioiodine

Huysmans DAKC, Hermus ARMM, Corstens FHM, Barentsz JO, Kloppenborg PWC

Annals of Internal Medicine 1994;121:757–62

Objective: To evaluate the effectiveness of radioiodine therapy as an alternative for surgery in elderly patients with a large, compressive goiter using objective methods for measuring thyroid volume and tracheal compression.
Design: Prospective study.
Setting: University hospital in the Netherlands.
Patients: 19 patients aged 66 ± 14 years (mean $\pm$ SD) with a large, compressive multinodular goiter who had a high operative risk or refused to have thyroid surgery.
Intervention: A single intravenous dose of ^{131}I at 2.6 ± 1.0 GBq (70 ± 28 mCi; 3.7 MBq or 100 μCi/g of thyroid tissue), followed by daily administration of L-thyroxine in doses that did not suppress thyroid-stimulating hormone.
Measurements: Clinical evaluation and measurements of thyroid volume, maximal tracheal deviation, and the smallest cross-sectional area of the tracheal lumen with magnetic resonance imaging before and 1 year after ^{131}I treatment.
Results: No exacerbation of compressive symptoms after ^{131}I therapy was observed. Thyroid volume was 269 ± 153 mL before treatment and 154 ± 73 mL 1 year after treatment ($p < 0.001$). Thyroid volume was reduced $40\% \pm 15\%$ (range, 19% to 68%). Maximal tracheal deviation (1.9 ± 0.8 cm before and 1.5 ± 0.7 cm 1 year after therapy) had decreased by $20\% \pm 20\%$ (range, -4% to 73%; $p < 0.001$), and the smallest cross-sectional area of the tracheal lumen (0.78 ± 0.38 cm^2 before and 1.04 ± 0.48 cm^2 1 year after therapy) had increased by $36\% \pm 38\%$ (range, -3% to 125%; $p < 0.001$). Clinical signs and symptoms improved in 8 of 12 patients with dyspnea and inspiratory stridor and in both patients with compression of the superior vena cava.
Conclusions: Therapy with ^{131}I is an effective alternative to surgery for elderly patients with a large, compressive multinodular goiter.

7.1 Introduction

Surgical treatment is considered standard therapy for patients with a large, compressive multinodular goiter. However, although thyroid surgery leads to rapid tracheal decompression in most patients [1], it is not without risk [2–4]. Moreover, goiters recur after surgery in 10% to 20% of patients [5, 6]. Surgical morbidity (hemorrhage and infection, dyspnea caused by tracheomalacia or recurrent nerve damage, and hypoparathyroidism) and mortality are highest in patients with very large goiters and in those who have another operation [2, 4, 7]. In elderly patients, surgical treatment of a large, compressive goiter may be contraindicated because of cardiac or pulmonary disease; in addition, some patients refuse to be operated on. Berghout and colleagues [8] reported that in about half of their patients with a smaller nontoxic goiter (mean volume, 53 mL), thyroid volume decreased by 25% during treatment with L-thyroxine in thyroid-stimulating hormone (TSH)-suppressive doses. The efficacy of this treatment in large, compressive nodular goiters is probably much lower [9]. Radioiodine therapy may be an alternative for these patients. However, most clinicians are reluctant to use radioiodine in patients with a large, compressive multinodular goiter because until now, reduction of thyroid volume by radioiodine therapy had not been assessed with objective methods and reversibility of compressive symptoms had not been shown. We treated 21 patients with a large, compressive multinodular goiter using a single dose of radioiodine followed by daily administration of a nonsuppressive dose of L-thyroxine. Before and 1 year after radioiodine treatment, anatomical assessment was done by magnetic resonance imaging (MRI). This technique allows high-precision measurements of thyroid volume, tracheal compression, and tracheal deviation [10]. We used medical interview, physical examination, and pulmonary function tests to assess functional results.

7.2 Methods

Patients

Twenty-one patients, 18 women and 3 men aged 67 ± 14 years (mean $\pm$ SD; range, 46 to 86 years), were entered into the study. All patients had a large, multinodular goiter (greater than 100 mL) that caused tracheal compression. Multinodularity was confirmed by thyroid scintigraphy that was done 2 hours after intravenous administration of 37 MBq (1 mCi) of sodium iodide (^{123}I). Nineteen patients had intrathoracic extension of the goiter of more than 2 cm,

as shown on MRI. One patient had a completely intrathoracic goiter. There was no clinical suspicion of thyroid malignancy in any patient. In two patients with a large cold nodule, examination of fine-needle aspiration biopsy specimens showed no signs of malignancy. Radioiodine treatment was chosen because of the high operative risk primarily related to cardiopulmonary disease or because the patient refused to have surgery.

Seventeen patients were clinically euthyroid and had serum free thyroxine (fT_4) and total triiodothyronine (T_3) levels within the normal range of our laboratory (fT_4, 9.0 to 17.0 pmol/L; T_3 1.5 to 3.5 nmol/L). In five of these patients, the serum TSH level was clearly suppressed (<0.1 mU/L). For treatment of hyperthyroidism, four patients received a thyroid-blocking dose of methimazole, which was combined with L-thyroxine to prevent hypothyroidism. Thyroid surgery had been done in eight patients (in one patient twice and in another three times) 4 to 50 years before radioiodine treatment. One euthyroid patient had been treated with 1.1 GBq (40 mCi) of radioiodine for hyperthyroidism 4 years before entering into our study. In three of the euthyroid patients, previous TSH-suppressive treatment with L-thyroxine had not reduced goiter size and had been stopped 3 months before radioiodine treatment.

Radioiodine therapy

Radioiodine was given as a single intravenous dose on an in-patient basis. Corticosteroids were not administered routinely. The administered activity was aimed at delivering 3.7 MBq (100 μCi) of ^{131}I/g of thyroid tissue retained at 24 hours according to the following formula [11]: administered activity (GBq) = thyroid weight (g) × 0.37 / 24-hour thyroid radioactive iodide uptake (%). Twenty-four hours after patients orally ingested 7.4 MBq (200 μCi) of ^{131}I, we measured ^{131}I thyroid radioactive iodide uptake (normal range, 10% to 59%) and made a rectilinear thyroid scintigram. We estimated thyroid weight from the planimetric surface on the scintigram using the formula of Doering and Kramer [12]: thyroid weight (g) = 0.326 × (surface in $cm^2)^{3/2}$. After radioiodine therapy, euthyroid patients were treated with L-thyroxine to keep serum TSH levels below 1.5 mU/L. Hyperthyroid patients continued to receive the combination therapy with methimazole and L-thyroxine during the first 6 months after radioiodine therapy (patients did not receive methimazole for 3 days before and 3 days after therapy).

Assessment of anatomical and functional results

We assessed anatomical and functional measurements before and 1 year after radioiodine therapy. In a medical interview and physical examination, special

attention was paid to compressive symptoms and signs (such as inspiratory stridor, dyspnea, voice changes, and the Horner syndrome). The same observer measured maximal neck circumference and central venous pressure before and 1 year after radioiodine therapy. Blood samples were obtained for measurement of serum levels of TSH (Delfia hTSH Ultra, Wallac Oy, Turku, Finland), T_4 (in-house radioimmunoassay), T_3 (Amerlex-M T3, Kodak Clinical Diagnostics Ltd, Amersham, United Kingdom), fT_4 (SPAC fT_4, Byk-Sangtec Diagnostica, Dietzenbach, Germany) and thyroglobulin (IRMA-mat Thyroglobulin, Byk-Sangtec Diagnostica). We determined 24-hour thyroid radioactive iodide uptake as described above.

Thyroid volume was measured with MRI (Siemens Magnetom 63SP, Erlangen, Germany) operating at a field strength of 1.5 tesla. We obtained T_1-weighted images (TR = 270 ms, TE = 15 ms) by using a Helmholtz neck coil and covering the entire thyroid in the coronal, sagittal, and axial planes. The thyroid outline was drawn manually on each slice, and a computer program calculated the surface of the traced areas. To calculate the thyroid volume, we multiplied the sum of the traced surfaces in each plane by the slice distance (0.88 cm). Thyroid volume, as used hereafter, is the mean of the measurements in the three imaging planes. Precision of this method is high. In patients with a large, multinodular goiter, the intraobserver coefficient of variation is $2.2\% \pm 2.0\%$, and the interobserver coefficient of variation is $4.1\% \pm 2.2\%$ (10). We used axial MRI slices to measure the largest deviation of the center of the tracheal lumen from the midline (orientated on the center of the vertebral canal and the spinous processes and supraspinal ligaments). The smallest cross-sectional area of the tracheal lumen, a measurement of tracheal compression (13), was measured planimetrically in axial MRI slices. All measurements were done blinded.

We measured forced inspiratory volume in 1 second (FIV_1) as a functional index of upper-airway obstruction. We compared values of our patients with values obtained from age- and sex-matched normal persons (14). Reference values are described by the following equation: FIV_1 (mL) = ($-0.0025 \times$age in years$+0.69$) $\times$ total lung capacity (mL). An FIV_1 that was more than 20% less than the reference value was considered below normal. An otolaryngology specialist tested the vocal cord motility of all patients before and 1 year after radioiodine therapy.

Statistical analyses were done using the Wilcoxon sign-rank test for paired observations (p-values denoted as p) and the Spearman rank-correlation test (p-values denoted as p*). The mean values $\pm$ 1 standard deviation are given.

7.3 Results

After intravenous administration of ^{131}I in a dose of 2.6 ± 1.0 GBq (71 ± 26 mCi; range, 1.4 to 5.6 GBq or 37 to 150 mCi), patients were hospitalized for 5 to 21 days. We observed no exacerbation of compression symptoms after patients received radioiodine. Two patients had a sore throat that was probably caused by radiation sialadenitis or esophagitis, but spontaneous and complete recovery was reached within 4 weeks. We observed no symptoms or signs of thyrotoxicosis caused by radiation thyroiditis.

Of the 21 patients who entered the study, 19 could be evaluated 1 year after radioiodine therapy. An 84-year-old euthyroid woman had died of an unrelated cardiac cause 1 month after radioiodine therapy. A 67-year-old hyperthyroid woman had thyroid surgery because of insufficient relief of tracheal compression despite a second dose of ^{131}I that was given 7 months after the first dose (total dose, 6.4 GBq or 173 mCi). Thyroid volume was reduced 10% as measured by MRI at the time of operation (10 months after the first dose of ^{131}I), and the smallest cross-sectional area of the tracheal lumen and the FIV_1 had not changed.

Anatomical results

Table 7.1 shows anatomical results of the 19 patients who were evaluated before and 1 year after radioiodine therapy. Before therapy, thyroid volume as measured with MRI was 269 ± 153 mL (range, 109 to 825 mL). One year after radioiodine therapy, thyroid volume was 154 ± 73 mL (range, 57–381 mL; $p < 0.001$). Expressed as the percentage of pretreatment thyroid volume, reduction was $40\% \pm 15\%$ (range, 19% to 68%; Figure 7.1). Neck circumference decreased by 3 ± 2 cm (range, 0 to 8.0 cm). The circumference of one patient with a completely intrathoracic goiter decreased 0 cm. The decrease in neck circumference was significantly correlated with the percentage of volume reduction ($r = 0.557$; $p^* < 0.02$).

The maximal deviation of the trachea from the midline was 1.9 ± 0.8 cm (range, 0.2 to 3.1 cm) before and 1.5 ± 0.7 cm (range, 0.2 to 2.6 cm) 1 year after radioiodine therapy ($p < 0.001$). The mean decrease was $20\% \pm 20\%$ (range, -4% to 73%; Figure 7.1). In 13 patients, tracheal deviation decreased more than 10% (including a 20% to 30% decrease in 4 patients and a greater than 30% decrease in 4 patients).

The smallest cross-sectional area of the tracheal lumen was 0.78 ± 0.38 cm^2 (range, 0.29 to 1.70 cm^2) before therapy and 1.04 ± 0.48 cm^2 (range, 0.30 to 2.19 cm^2; $p < 0.001$) after therapy. The mean increase was $36\% \pm 38\%$ (range,

Table 7.1 *Results of treatment with radioiodine and L-thyroxine in 19 patients with a large, compressive multinodular goiter* *

Patient [a]	Age	Dose of ^{131}I		Thyroid volume [b]	Thyroid volume [c]			Smallest cross-sectional area tracheal lumen			Maximal tracheal deviation			Neck circumf.
				Before ^{131}I	Before ^{131}I	Decrease after ^{131}I		Before ^{131}I	Increase after ^{131}I		Before ^{131}I	Decrease after ^{131}I		Decrease after ^{131}I
	yr	GBq	(mCi)	ml	ml	ml	(%)	cm^2	cm^2	(%)	cm	cm	(%)	cm
1	67	2.2	(61)	158	258	77	(30)	0.67	0.24	(36)	2.2	0.0	(0)	1.0
2	55	2.2	(59)	182	181	123	(68)	0.75	0.60	(80)	2.9	0.8	(28)	3.0
3	86	1.6	(43)	116	203	53	(26)	0.71	−0.02	(−3)	1.6	0.4	(24)	2.0
4	46	2.8	(76)	183	232	88	(38)	1.36	0.25	(18)	2.4	0.2	(7)	2.0
5	83	4.3	(115)	358	231	60	(26)	0.29	0.01	(3)	2.3	−0.1	(−6)	3.5
6	58	2.6	(71)	310	253	130	(51)	1.70	0.49	(29)	1.1	0.3	(26)	3.5
7	60	3.2	(86)	363	457	201	(44)	0.53	0.16	(30)	1.6	0.0	(0)	4.5
8	67	1.5	(40)	108	109	24	(22)	0.97	−0.03	(−3)	0.8	0.3	(44)	3.0
9	48	1.9	(50)	225	223	63	(28)	0.74	0.38	(51)	0.2	0.0	(0)	0.0
10	80	2.6	(70)	188	190	55	(29)	0.55	0.02	(4)	3.1	0.5	(15)	1.0
11	72	2.2	(59)	328	193	79	(41)	0.45	0.06	(13)	1.8	0.2	(11)	1.0
12	73	1.8	(50)	359	316	167	(53)	0.58	0.41	(71)	2.7	0.9	(34)	7.5
13	46	2.8	(76)	250	280	54	(19)	1.09	0.17	(16)	1.9	0.2	(8)	2.5
14	62	2.6	(70)	217	164	85	(52)	0.62	0.77	(124)	1.8	0.5	(27)	3.0
15	81	3.1	(85)	351	286	159	(55)	0.55	0.65	(118)	1.4	0.2	(13)	4.5
16	52	1.4	(37)	179	170	52	(30)	1.51	0.18	(12)	2.2	0.3	(13)	0.5
17	82	5.6	(150)	1002	825	444	(54)	0.33	0.08	(24)	1.2	0.0	(0)	8.0
18	56	1.8	(49)	297	283	184	(65)	0.76	0.38	(50)	2.9	1.2	(40)	4.5
19	80	3.3	(90)	289	254	91	(36)	0.71	0.11	(15)	1.1	0.8	(71)	1.5
mean	66	2.6	(70)	288	269	115	(40)	0.78	0.26	(36)	1.9	0.3	(20)	3
SD	14	1.0	(28)	192	153	94	(15)	0.38	0.24	(38)	0.8	0.4	(20)	2

* Anatomical data obtained before and 1 year after radioiodine therapy. SD = standard deviation

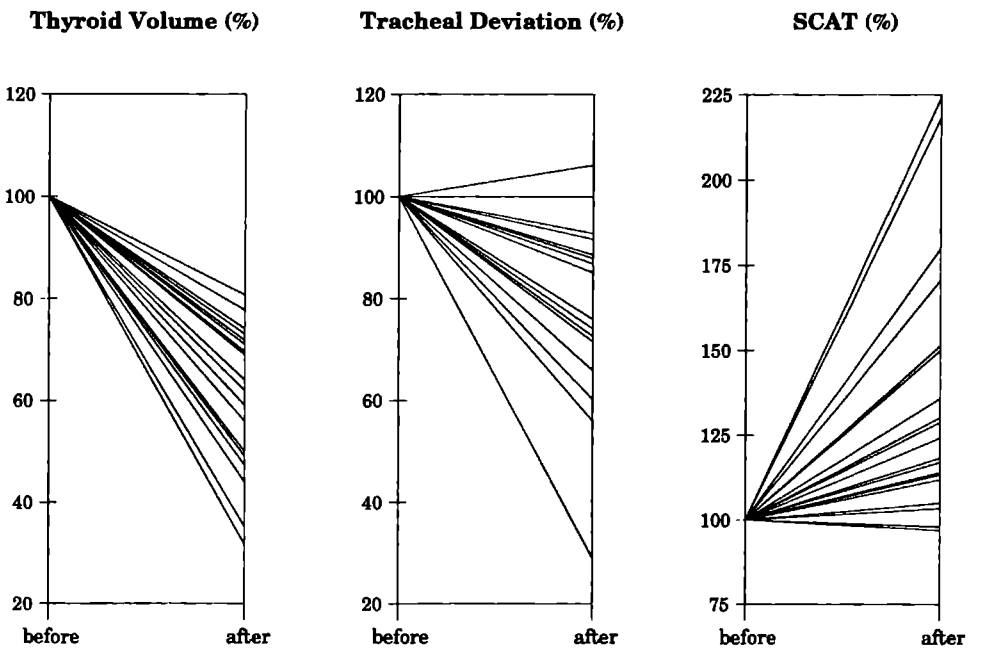
a Patients 1 to 16 were euthyroid, and patients 17 to 19 were hyperthyroid. Patients 1, 3, 4, 9, 10, 14, 18, and 19 previously had thyroid surgery. Patients 3, 5, and 10 had vocal cord paralysis before radioiodine therapy, due to previous surgery. Patient 9 had a completely intrathoracic goiter

b Determined by scintigraphy

c Determined by magnetic resonance imaging

−3% to 124%; Figure 7.1). We observed an increase of more than 10% in 15 patients (including an increase of 50% to 100% in 6 patients and an increase of more than 100% in 2 patients). In four patients, the smallest cross-sectional area of the tracheal lumen changed very little (<5%). Increase of the smallest cross-sectional area of the tracheal lumen was significantly correlated with the decrease of thyroid volume ($r = 0.727$; $p^* < 0.001$).

Figure 7.1 *Thyroid volume (left), maximal deviation of the tracheal center from the midline (middle), and smallest cross-sectional area of the tracheal lumen (SCAT; right) measured before and 1 year after radioiodine therapy in 19 patients with a large, compressive multinodular goiter. Data are expressed as percentages of pretreatment values*



Functional results

The FIV_1 was 2285 ± 1145 mL before therapy (range, 675 to 4450 mL) and 2515 ± 1129 mL after therapy (range, 775 to 4600 mL; $p < 0.01$). In 8 of 18 patients, the FIV_1 increased more than 10% (11% to 20% in 3 patients, 21% to 30% in 2 patients, 31% to 50% in 2 patients, and 120% in 1 patient). Before radioiodine treatment, FIV_1 was below normal (that is, more than 20% less than the reference value) in 6 patients. One year after therapy, it had returned to normal in 2 of these patients and had considerably improved in 2 others. The 2 patients in whom FIV_1 had not improved had vocal cord paralysis caused by previous surgery. Symptoms of superior vena cava obstruction disappeared in 1 patient (Figure 7.2), and elevated central venous pressure returned to normal in another patient.

Figure 7.2 *Patient 17 before and 1 year after treatment with 5.6 GBq (150 mCi) of ^{131}I. Note the distended neck veins and edematous face as signs of compression of the superior vena cava before therapy (A) and their improvement 1 year after therapy (B). Published by permission of patient*

Table 7.2 shows the effects of radioiodine treatment on subjective patient reports that were related to compression of the trachea and esophagus. Dyspnea and stridor improved in 8 of 12 patients, and dysphagia improved in 7 of 8 patients. As reported by the patients, the most important subjective improvement was achieved within the first 3 months after radioiodine treatment.

Table 7.2 *Functional results of treatment with radioiodine and L-thyroxine in 19 patients with a large, compressive multinodular goiter* *

	Before ^{131}I therapy	1 year after ^{131}I therapy		
		No change [a]	Improved	Cured
Dyspnea	12	4	1	7
Inspiratory stridor	12	4	2	6
Dysphagia	8	1	1	6

* Numbers of patients are given; functional data obtained before and 1 year after radioiodine therapy

[a] Two of the patients in whom dyspnea and stridor were unchanged after therapy had vocal cord paralysis caused by previous thyroid surgery

Thyroid function after radioiodine therapy

Hyperthyroidism was eliminated within 6 months in the four hyperthyroid patients. Patient 9, who was clinically euthyroid before therapy and had normal fT_4 and T_3 levels and a suppressed TSH level, developed hyperthyroidism 7 months after radioiodine treatment. At that time, antithyroglobulin and antimitochondrial antibodies were negative. The 3-hour thyroid radioactive iodide uptake was 64% (normal range, 5% to 30%), and examination of a scintigraph of the thyroid showed an almost diffuse ^{123}I uptake in the whole thyroid gland. The patient was treated with methimazole for 9 months and received a second dose of radioiodine (1.8 GBq or 67 mCi) 16 months after the first radioiodine treatment. We could not accurately assess the effects on thyroid function in the other euthyroid patients because of L-thyroxine treatment after radioiodine therapy. The 24-hour thyroid radioactive iodide uptake was $40\% \pm 15\%$ (range, 24% to 72%) before radioiodine treatment and $19\% \pm 14\%$ (range, 2% to 58%) 1 year after therapy. One year after therapy, four patients had a 24-hour thyroid radioactive iodide uptake that was less than normal (<5%). We observed no consistent changes in serum thyroglobulin levels.

7.4 Discussion

Our study clearly shows the efficacy of treatment with radioiodine in patients with a large, compressive multinodular goiter. One year after radioiodine therapy, thyroid volume as measured with MRI was reduced by 40%. Even more clinically important is our finding of a significant decrease of tracheal compression after radioiodine treatment: We observed a widening of the tracheal lumen at its narrowest point by an average of 36%. The tracheas of 15 of 19 patients widened more than 10%, and deviation of the trachea from the midline decreased more than 10% in 13 of 19 patients. Improvement of these anatomical measurements was accompanied by improvement of clinical signs and symptoms in 8 of 12 patients with dyspnea and inspiratory stridor. Furthermore, symptoms of obstruction of venous flow improved in both patients with compression of the superior vena cava. Forced inspiratory volume in 1 second improved by more than 10% in 8 patients.

Few other reports have described the results of radioiodine therapy on volume reduction of large goiters [15–18]. However, the techniques used to estimate volume reduction in these studies — palpation, measurement of maximal neck circumference, and planar thyroid scintigraphy — are notoriously imprecise; none of these investigators evaluated tracheal compression with objective methods. Having used ultrasound to measure thyroid volume, Nygaard and colleagues [19] recently reported effects of radioiodine treatment in small nontoxic goiters (median volume, 73 mL). These investigators observed a 42% volume reduction 1 year after radioiodine therapy. However, ultrasound cannot be used for large goiters because of frequent intrathoracic extension [20, 21]. We therefore used MRI, which is not limited by intrathoracic extension of the goiter, to evaluate the effect of radioiodine treatment in large goiters (mean volume, 269 mL).

The routine prescription of L-thyroxine after radioiodine treatment prevented us from accurately assessing the rate of hypothyroidism. However, only 4 of 19 patients had a below-normal 24-hour radioiodine uptake 1 year after therapy. Nygaard and colleagues [19] also observed a relatively low rate of hypothyroidism. They calculated a 22% rate of hypothyroidism after 5 years using the life table method. In contrast, Verelst and colleagues [18], despite the use of doses of radioiodine similar to those used by Nygaard and coworkers, found that 30% of the patients studied had hypothyroidism 3 years after therapy; after 8 years, all living patients were hypothyroid. Hyperthyroidism developed in one of our euthyroid patients 7 months after radioiodine treatment. Other investigators [19, 20] have also observed this late development of hyperthyroidism and

have suggested that it is an autoimmune phenomenon triggered by irradiation-induced antigen release [22]. Furthermore, patients should be watched carefully for signs of thyrotoxicosis caused by radiation thyroiditis, especially in the first weeks after radioiodine therapy for a large goiter.

Radioiodine is a widely accepted treatment for thyrotoxicosis. However, most clinicians are reluctant to administer radioiodine to reduce the volume of large, compressive goiters for fear of exacerbating compressive symptoms and because of concern for too-high absorbed doses of radiation. We observed no exacerbation of compression symptoms necessitating corticosteroid medication after radioiodine treatment. This is in accordance with the experience of other investigators [15–19]. Thus, radiation thyroiditis causing thyroid swelling and increase of compression symptoms appears to be rare. In our study, patients received 3.7 MBq (100 μCi) of ^{131}I/g of thyroid tissue, a dose commonly used for treating hyperthyroidism caused by diffuse or nodular goiter [23]. For toxic nodular goiter, even higher doses are frequently used [24–26]. In a separate dosimetric study in patients with large toxic and large nontoxic multinodular goiters (mean thyroid volume, 200 mL in both groups), we calculated mean radiation absorbed doses of 80 Gy (8000 rad) in the thyroid, 4 Gy (400 rad) directly near the thyroid, and 0.05 to 0.6 Gy (5 to 60 rad) in other tissues; we observed no significant differences between hyperthyroid and euthyroid patients. The effective dose to the whole body was 4 sievert (400 rem) for both hyperthyroid and euthyroid patients. The observed absorbed doses in extrathyroidal tissues are higher than those after radioiodine treatment of small goiters. The risk for leukemia and cancer after radioiodine therapy in patients with small goiters does not appear to be elevated [27]. Such data are not available for large goiters treated with higher doses of radioiodine. Because radiation-induced carcinogenesis is a late effect, this risk is less important in elderly patients. In view of these considerations, we believe radioiodine treatment of large goiters should be restricted to elderly patients.

Our study has some limitations. First, follow-up was restricted to 1 year after radioiodine treatment. Further follow-up will show whether the excellent anatomical and functional results, as shown in our study, persist. In this respect, it is of interest that, in the study of Nygaard and colleagues [19], the volume of small nontoxic goiters was reduced 42% 1 year after radioiodine therapy but was reduced 60% after a median follow-up of 60 months. Second, we cannot exclude with certainty the possibility that the observed effects of radioiodine therapy are influenced by the use of L-thyroxine after radioiodine treatment in the euthyroid patients or by the combination therapy of methimazole and L-thyroxine in the hyperthyroid patients. It is unlikely, however, that the routine prescription of

L-thyroxine after radioiodine therapy in our study contributed substantially to the observed reduction in thyroid volume because this medication was administered in non-TSH-suppressive doses and because even TSH-suppressive doses are not likely to effectively reduce the volume of large, multinodular goiters [9]. Methimazole, which shortens the biological half-life of radioiodine in the thyroid, could have negatively affected the effectiveness of radioiodine. However, in three of the four hyperthyroid patients, thyroid volume was reduced more than 35% 1 year after therapy. Third, the administered amounts of radioiodine in our study were not based on accurate measurements of the functional volume within the thyroid gland. Single-photon emission computed tomography or positron emission tomography may prove to be useful tools for more accurate planning of therapeutic doses of radioiodine for nodular goiters. The accuracy of these techniques and the therapeutic surplus value of more accurate measurements of the functional volume of nodular goiters should be evaluated in further studies.

In conclusion, our study shows a 40% reduction of thyroid volume and clinically significant decompression of vital structures 1 year after treatment with radioiodine and L-thyroxine in patients with a large, compressive goiter. We recommend this treatment as an effective alternative for surgery in elderly patients.

Acknowledgments

The authors thank the technicians of the departments of Nuclear Medicine, Radiology and Pulmonary Medicine for their assistance; the nursing staff of unit E30 for their care of the patients; and Professor H. Folgering and Dr. J. Festen for their advice.

7.5 References

1 Miller MR, Pincock AC, Oates GD, Wilkinson R, Skene-Smith H. Upper airway obstruction due to goitre: detection, prevalence and results of surgical management. *Q J Med* 1990;74:177–88

2 Sailer R, Horster F. Intra- und Postoperative Komplikationen. *In: Sailer R, Horster F, eds. Chirurgie der Schilddrüse. Stuttgart, Germany: Enke* 1986:77–80

3 Foster RS Jr. Morbidity and mortality after thyroidectomy. *Surg Gynecol Obstet* 1978;146:423–9

4 Studley JG, Lynn J. Surgical anatomy of the thyroid gland and the technique of thyroidectomy. *In: Lynn J, Bloom SR, eds. Surgical Endocrinology. Oxford: Butterworth-Heinemann* 1993:231–40

5 Berghout A, Wiersinga WM, Drexhage HA, van Trotsenburg P, Smits NJ, van der Gaag RD, *et al.* The long-term outcome of thyroidectomy for sporadic non-toxic goitre. *Clin Endocrinol (Oxf)* 1989;31:193–9

6 Geerdsen LP, Frølund L. Recurrence of nontoxic goitre with and without postoperative thyroxine medication. *Clin Endocrinol (Oxf)* 1984;21:529–33

7 Weitensfelder W, Lexer G, Aigner H, Fellinger H, Trattnig J, Grünbacher G. Die langfristige laryngoskopische Nachkontrolle bei Einschränkung der Stimmbandmotilität nach Strumaoperation [Long-term laryngoscopic follow-up in vocal cord paralysis following struma surgery]. *Chirurg* 1989;60:29–32

8 Berghout A, Wiersinga WM, Drexhage HA, Smits NJ, Touber JL. Comparison of placebo with L-thyroxine alone or with carbimazole for treatment of sporadic nontoxic goitre. *Lancet* 1990;336:193–7

9 Shimaoka K, Sokal JE. Suppressive therapy of nontoxic goiter. *Am J Med* 1974; 57:576–83

10 Huysmans DA, de Haas MM, van den Broek WJ, Hermus AR, Barentsz JO, Corstens FH, *et al.* Magnetic resonance imaging for volume estimation of large multinodular goitres: a comparison with scintigraphy. *Br J Radiol* 1994;67:519–23

11 DeGroot LJ. Graves' disease diagnosis and treatment. Multinodular goiter. *In: DeGroot LJ, Stanbury JB, eds. The Thyroid and Its Diseases, 4th ed. New York: Wiley* 1975:314–67 and 637–65

12 Doering P, Kramer K. Die Bestimmung des Schilddrüsengewichtes mit der Szintigraphie nach Gabe von Radiojod: Ein Beitrag zur Dosierung des Radioisotopes. *Strahlenther* 1958;105:245–59

13 Rohrer F. Der Strömungswiderstand in den menschlichen Atemwegen und der Einfluß der unregelmäßigen Verzweigung des Bronchialsystems auf den Atmungsverlauf vescheidenen Lungenbezirken. *Pflügers Arch ges Physiol* 1915;162:225–99

14 Tammeling GJ. Relationships between and reference values for lung volumes. *In: Tammeling GJ, Quanjer PH, eds. Contours of Breathing 1. Ingelheim am Rhein: Boehringer* 1979:76–7

15 Keiderling Von W, Emrich D, Hauswaldt Ch, Hoffmann G. Ergebnisse der Radiojod-Verkleinerungstherapie euthyreoter Strumen. *Dtsch Med Wochenschr* 1964; 89:453–7

16 Frey KW. Früh- und Spätergebnisse der ^{131}Jod-Therapie der blanden Struma im Kropfendemiegebiet Südbayerns. *Fortschr Röntgenstr* 1979;130:172–4

17 Kay TW, d'Emden MC, Andrews JT, Martin FIR. Treatment of non-toxic multinodular goiter with radioactive iodine. *Am J Med* 1988;84:19–22

18 Verelst J, Bonnyns M, Glinoer D. Radioiodine therapy in voluminous multinodular non-toxic goitre. *Acta Endocrinol (Copenh)* 1990;122:417–21

19 Nygaard B, Hegedüs L, Gervil M, Hjalgrim H, Søe-Jensen P, Mølholm Hansen J. Radioiodine treatment of multinodular non-toxic goitre. *BMJ* 1993;307:828–32

20 Berghout A, Wiersinga WM, Smits NJ, Touber JL. The value of thyroid volume measured by ultrasonography in the diagnosis of goitre. *Clin Endocrinol (Oxf)* 1988;28:409–14

21 Hegedüs L. Thyroid size determined by ultrasound. Influence of physiological factors and non-thyroidal disease. *Dan Med Bul* 1990;37:249–63

22 Kay TW, Heyma P, Harrison LC, Martin FI. Graves' disease induced by radioactive iodine. *Ann Intern Med* 1987;107:857–8

23 Cooper DS. Treatment of thyrotoxicosis. *In: Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid, 6th ed. Philadelphia: Lippincott* 1991:887–916

24 Bliddal H, Hansen JM, Rogowski P, Johansen K, Friis T, Siersbaek-Nielsen K. ^{131}I treatment of diffuse and nodular toxic goitre with or without antithyroid agents. *Acta Endocrinol (Copenh)* 1982;99:517–21

25 Hamburger JI, Hamburger SW. Diagnosis and management of large toxic multinodular goitres. *J Nucl Med* 1985;26:888–92

26 Berding G, Schicha H. Ergebnisse der Radiojodtherapie der manifesten Hyperthyreose und der autonomen Struma mit Euthyreose [Results of radioiodine of manifest hyperthyroidism and autonomous struma with euthyroidism]. *Nuklearmedizin* 1990;29:158–165

27 Holm LE, Hall P, Wiklund K, Lundell G, Berg G, Bjelkengren G, *et al.* Cancer risk after iodine-131 therapy for hyperthyroidism. *J Natl Cancer Inst* 1991;83:1072–7

Chapter

eight

Dosimetry and risk estimates of radioiodine therapy of large, multinodular goiters

Submitted for publication:

Dosimetry and Risk Estimates of Radioiodine Therapy of Large, Multinodular Goiters

Huysmans DAKC, Buijs WCAM, Van de Ven MTP,
Van den Broek WJM, Kloppenborg PWC,
Hermus ARMM, Corstens FHM

In patients with a large, multinodular goiter (>100g), radiation absorbed doses in the thyroid, surrounding tissues and remainder of the body were estimated after therapeutic administration of ^{131}I (3.7 MBq/g of thyroid tissue retained at 24 h).

Methods: Thermoluminescent dosimeter (TLD) measurements were performed in 23 patients (12 eu- and 11 hyperthyroid; thyroid weight 222 ± 72 g (mean $\pm$ SD); administered activity 2.1 ± 0.9 GBq) on the skin over the thyroid, over the submandibular gland and over the parotid gland. Thyroid radioactivity measurements were done daily in 6 eu- and 6 hyperthyroid patients (thyroid weight 204 ± 69 g; administered activity 1.9 ± 0.9 GBq). An iodine biokinetic model and the MIRD method were used to estimate absorbed doses in organs. Cancer risks were calculated using ICRP Publication 60.

Results: Cumulated absorbed doses on the skin (TLD measurements) were 4.2 ± 1.4 Gy over the thyroid, 1.2 ± 0.6 Gy over the submandibular gland and 0.4 ± 0.2 Gy over the parotid gland. All these values were significantly correlated with the amount of radioiodine retained in the thyroid at 24 h and no significant differences were present between eu- and hyperthyroid patients. Absorbed doses in the thyroid of 84 ± 22 Gy for eu- and 83 ± 15 Gy for hyperthyroid patients were calculated (thyroid radioactivity measurements). Extrathyroidal absorbed doses (averages of 12 patients) were 0.88 Gy in the urinary bladder, 0.57 Gy in the small intestine, 0.38 Gy in the stomach, and ranged from 0.05 to 0.30 Gy in other organs (no significant differences between eu- and hyperthyroid patients). A 1.6% life-time risk of development of cancer outside the thyroid gland was calculated. When applied to people of 65 years and older the estimated risk is approximately 0.3%.

Conclusions: These data may help in choosing the treatment in the individual patient with a large, multinodular goiter, who has to be treated for hyperthyroidism or compressive problems. In younger patients surgery may be preferred. However, for elderly patients and patients with cardiopulmonary disease, the profits of non-invasive radioiodine treatment will outweigh the life-time risk of this mode of therapy.

8.1 Introduction

Surgery is standard therapy for patients with a large, toxic or nontoxic, compressive goiter. However, it is not without risk, especially in elderly patients with cardiopulmonary disease [1, 2, 3]. Radioiodine, a widely accepted treatment for patients with toxic, non-compressive goiters, is an alternative for these patients. In a recent study, we have shown that radioiodine therapy can induce an average reduction in thyroid volume of 40% after one year and a significant widening of the tracheal lumen in patients with a large, compressive multinodular goiter [4]. However, a cause for reluctancy to treat these patients with radioiodine may be a concern for too-high radiation absorbed doses. Many commonly used dosage schedules for radioiodine therapy are aimed at delivering a certain amount of radioiodine per gram of thyroid tissue retained in the thyroid gland at 24 hours. The use of such a dosage schedule implies that large amounts of radioiodine are administered to patients with a large, nodular goiter.

The present study is focused on the dosimetric aspects of radioiodine therapy in patients with such a large goiter. We have estimated absorbed doses in the thyroid, in tissues directly near the thyroid and in tissues and organs in the remainder of the body after therapeutic administration of radioiodine in hyperthyroid and in euthyroid patients with a large, multinodular goiter. Thermoluminescent dosimetry was used to estimate the radiation burden of tissues directly near the thyroid gland. Estimations of absorbed doses in the thyroid and in the remainder of the body were made using thyroid radioactivity measurements and a model of iodine kinetics in the body as described by Robertson and Gorman [5]. Risks of the development of radiation-induced cancer were assessed, based on the 1990 Recommendations of the International Commission on Radiological Protection [6].

8.2 Patients and methods

Patients and radioiodine treatment

Twenty three consecutive patients with a multinodular goiter of more than 100 g, as estimated from palpation and planar thyroid scintigraphy [7], were treated with radioiodine. The diagnosis of multinodular goiter was based on the presence of one or more thyroid nodules at palpation and an irregular distribution of [^{123}I] or [^{131}I] sodium iodide on a thyroid scan. Patients with a solitary hot nodule were excluded. In the 11 patients with toxic multinodular goiter the primary aim of radioiodine therapy was to treat hyperthyroidism. Eight of them

had compressive symptoms. All euthyroid patients (n = 12) sought treatment for compressive symptoms. In these patients radioiodine therapy was chosen because of contraindications for surgery (n = 8; mainly because of cardiopulmonary disease) or refusal of the patient to undergo surgery (n = 4). Patients were classified as euthyroid when they had serum free thyroxine (fT_4) and triiodothyronine (T_3) levels within the normal range of our laboratory (fT_4, 9.0–17.0 pmol/l; T_3, 1.5–3.5 nmol/l) and were not taking antithyroid or thyromimetic drugs. The serum level of thyroid-stimulating hormone (TSH) was subnormal (<0.4 mU/l) in seven of them. In two euthyroid patients prior TSH-suppressive treatment with L-thyroxine had failed to diminish goiter size. L-thyroxine had been withdrawn 2 months before radioiodine treatment in these patients. All hyperthyroid patients used methimazole and L-thyroxine. They did not receive methimazole for 3 days before and 3 days after radioiodine therapy. Radioiodine was given as a single intravenous dose on an in-patient basis. The administered activity was aimed at delivering 3.7 MBq of ^{131}I per gram of thyroid tissue retained at 24 hours, according to the formula: administered activity (GBq) = thyroid weight (g) × 0.37 / 24-hour thyroid radioactive iodide uptake (%) [8]. Thyroid radioactive iodide uptake (RAIU) was measured 24 hours after oral ingestion of 7.4 MBq (200 μCi) of ^{131}I (normal range 10%–59%). The thyroid weight was estimated from the planimetric surface on a rectilinear thyroid scintigram using the formula of Doering and Kramer: thyroid weight (g) = 0.326 × (surface in $cm^2)^{3/2}$ [7].

Thermoluminescent dosimeter measurements; dosimetric calculations

Thermoluminescent dosimeter (TLD) measurements were performed following the therapeutic administration of radioiodine in 12 euthyroid and in 11 hyperthyroid patients. Two freshly annealed TLDs (LiF TLD 100, Harshaw, Ohio) sealed in a thin polyethylene bag were positioned with sticking plaster on the skin on each of the following three locations: directly over the thyroid gland, over the submandibular gland and over the parotid gland. The TLD on the thyroid gland was placed over the center of the most prominent nodule, which was checked not to be "cold" on thyroid scintigraphy. Distances between the TLDs on the salivary glands and the palpated ipsilateral top of the thyroid were measured. The TLDs were left in position for 24 hours, and replaced daily for 5 to 15 days after the therapeutic administration of radioiodine. After preannealing, TLDs were read for light output (in nanocoulombs) on a TLD reader under dry N_2 (Harshaw Model 4000, Ohio, software WINTLDM 2.1). The calibration factor of TLDs for the gamma irradiation of ^{131}I, as checked *in vitro*, was 100 microgray per nanocoulomb (μGy/nC). From a previous study [4] in patients with a

large, multinodular goiter (nine of whom also participated in the present study) it appeared that the distance between the surface of the thyroid and the surface of the skin, as determined from axial magnetic resonance imaging slices, was more than 5 mm. Therefore, the contribution of beta irradiation was assumed to be negligible on the surface of the skin.

TLD measured values from day 2 onward were fitted monoexponentially and extrapolated to infinity. The measured values and the integral of the extrapolated function were summed for each location in order to determine cumulated absorbed doses on the skin (Gy).

Thyroid radioactivity measurements; dosimetric calculations; risk estimates

In 6 euthyroid and in 6 hyperthyroid patients, thyroid radioactivity measurements were performed every 24 hours after the therapeutic administration of radioiodine for 7 to 14 days. A 3" × 3" NaI(Tl) detector was used with a lead-shield placed in front of it in order to reduce the count rate and avoid dead-time effects. Measurements were corrected for a standard with a known activity of ^{131}I and all values were corrected for background radioactivity, for thyroid radioactivity from ^{131}I previously injected for diagnostic purposes and for physical decay.

Thyroid radioactivity measurements were implemented in a simplified model for iodine biokinetics as described by Robertson and Gorman [5]. In this model, intravenously administered radioiodide is removed from the extrathyroidal inorganic iodide compartment (B) by excretion into the urinary iodide compartment (U), with fractional removal rate r_1 (in h^{-1}), and by uptake into the thyroid (T), with fractional uptake rate r_2 (in h^{-1}). In the thyroid radioiodide is incorporated in thyroglobulin. A 24 hour delay in the secretion of radioiodinated thyroid hormones is assumed [5]. After that time, the loss of radioactivity from the thyroid into the compartment of extrathyroidal radioiodinated thyroid hormone (P) is indicated by the fractional secretion rate r_3 (in h^{-1}). Degradation of the radioiodinated thyroid hormone is assumed to be instantaneous [5]. The rate of (renal) excretion of radioiodide resulting from thyroid hormone degradation is supposed to equal that of the administered inorganic iodide. The model does not take into account re-uptake into the thyroid of radioiodide resulting from thyroid hormone degradation outside the thyroid. A system of differential equations, using the three rate constants, r_1, r_2 and r_3, and the physical decay constant λ (0.00359 h^{-1}) describes the rates of changes of radioactivity in the four compartments (B, T, U and P). The solutions of the differential equations describe the fractional activities, *i.e.* the fractions of the administered activity at

time t in each of the compartments. These fractional activities are integrated in order to obtain the cumulated (time-integrated) fractional activities (cumulated activity per MBq of administered activity in MBq.h/MBq, *i.e.* in h; this parameter is also referred to as residence time) in each of the four compartments (Appendix, formulas 1–4). Time-integrated activities resulting from the total administered activities of radioiodine are referred to as cumulated activities (in MBq·h).

Serum creatinine levels were within the normal range in all patients. Therefore, an r_1 of 0.072 h^{-1} based on a normal renal function was assumed for all patients in our study [9]. The r_2 was calculated from the radioactivity measurement at 24 hours and from r_1 (Appendix, formula 5). Thyroid radioactivity measurements from day 2 onward (corrected for physical decay) were fitted as a monoexponential function. The rate constant of this function was used as r_3.

In the biokinetic model of Robertson and Gorman [5] the extrathyroidal thyroid hormone and inorganic iodide compartments are combined and assumed to be evenly distributed throughout the body, outside the thyroid and urinary bladder. We made the following amendments to the biokinetic model based on data in MIRD pamphlet no. 12 and MIRD report no. 5 [10, 11]. Of the extrathyroidal inorganic iodide compartment 15% was assumed to be located in the stomach and 17% in the small intestine. Of the extrathyroidal thyroid hormone compartment 40% was assumed to be located in the liver (and, proportional to the weight of the liver, 2.4% of the inorganic iodide compartment). Corresponding percentages of the residence times in the extrathyroidal inorganic iodide and thyroid hormone compartments were assigned to the stomach, small intestine and liver. The remaining parts of these residence times were assigned to the "total body" (*i.e.* evenly distributed throughout the body outside the thyroid, urinary bladder, stomach, small intestine and liver). In order to obtain the residence time in the urinary bladder, the cumulated fractional activity in the urine was corrected for voiding with a voiding interval of 4 hours.

Radiation absorbed doses in organs were calculated using the MIRD method with tabulated S values for adults (*i.e.* the mean radiation absorbed dose in a target organ per unit cumulated activity in a source organ) [12]. The calculated residence times in the source organs thyroid, urinary bladder, stomach, small intestine and "total body" were entered in the MIRDOSE2 computer program (Oak Ridge, Tennessee). In all patients absorbed doses in the thyroid, as calculated in the MIRDOSE2 program, were corrected for the ratio normal thyroid weight (20 g) / measured thyroid weight.

ICRP Publication 60 [6] was used to estimate the risk of radiation-induced cancer in our patients. In ICRP Publication 60, absorbed doses weighted by

a radiation factor (which is 1 for radiopharmaceuticals) are called equivalent doses (H; in sievert, Sv) [6]. The sum of the fatal cancer risk (estimated at 5%/Sv), non-fatal cancer risk (estimated at 1%/Sv) and the risk of severe hereditary effects (estimated at 1.3%/Sv) is 7.3% per sievert total body irradiation and is called the total detriment [6]. These probability coefficients are applicable to all equivalent doses resulting from absorbed doses below 0.2 Gy and from higher absorbed doses when the dose rate is less than 0.1 Gy per hour. The relative importance of each of the various organs in contributing to this detriment is expressed by its weighting factor W_T [6]. The detriment for each organ is expressed as $W_T \times 7.3\%/Sv$ organ dose. The weighting factor for the gonads applies for 90% to the risk of severe hereditary effects and for only 10% to the gonadal (especially ovarian) cancer risk. For other organs the weighting factor only applies to the cancer risk. Furthermore, the values for tissue weighting factors were used to determine the effective dose which is the sum of the weighted equivalent doses in all the tissues and organs of the body (effective dose = $\sum W_T \cdot H_T$) [6]. Only the contributions of the organs and tissues outside the thyroid were summed, because equivalent and effective doses are not applicable to high doses as received by the thyroid during radioiodine therapy.

Statistical analyses

The mean values $\pm$ SD are given. Statistical analyses were done using the Mann-Whitney U test for unpaired observations (p-values denoted as p), the Wilcoxon sign-rank test for paired observations (p-values denoted as p^*) and the Spearman rank correlation test (p-values denoted as p^{**}). The level of significance was 0.05.

8.3 Results

For detailed information on the effectiveness of radioiodine treatment for large, multinodular goiters with respect to reduction of thyroid volume and decompression of vital structures the reader is referred to a recently published study from our group [4]. Suffice it to mention here, that in the present group of patients thyroid volume reduction was satisfactory and that only one patient had to be treated with a second dose of radioiodine because of persistent hyperthyroidism.

Thermoluminescent dosimeter measurements

Table 8.1 shows patient characteristics and data of TLD measurements on the skin over the thyroid, the submandibular and the parotid gland in 12 eu- and 11 hyperthyroid patients.

Table 8.1 *Patient characteristics and data of thermoluminescent dosimetry measurements after radioiodine treatment of euthyroid and hyperthyroid patients with a large multinodular goiter (>100 g). The mean values ± SD are given (in parentheses ranges are given)*

	Euthyroid		Hyperthyroid		
Number of patients	12		11		
Age (years)	62 ± 12	(44–81)	71 ± 8	(57–82)	
Female : male ratio	11 : 1		8 : 3		
Thyroid weight(g)	221 ± 81	(122–351)	224 ± 65	(130–312)	
24h RAIU (%)	36 ± 11	(21–56)	51 ± 14	(32–78)	[a]
Administered activity of ^{131}I (GBq)	2.3 ± 0.8	(1.2–4.0)	1.8 ± 0.8	(0.8–3.3)	
Cumulated dose on skin thyroid (Gy)	4.4 ± 1.5	(2.4–7.2)	4.1 ± 1.4	(2.0–6.3)	
Cumulated dose on skin submandibular gland (Gy)	1.2 ± 0.6	(0.5–2.4)	1.3 ± 0.6	(0.5–2.0)	
Cumulated dose on skin parotid gland (Gy)	0.3 ± 0.1	(0.2–0.8)	0.4 ± 0.1	(0.2–0.7)	
Distance from thyroid to submandibular gland (cm)	4.7 ± 2.0	(2.5–7.5)	4.3 ± 1.7	(2.5–7.5)	
Distance from thyroid to parotid gland (cm)	10.7 ± 1.8	(8.5–13.5)	10.5 ± 2.0	(8.0–13.5)	
TLD measured effective half-time thyroid (days)	6.1 ± 0.8	(4.4–7.3)	5.5 ± 0.7	(4.2–6.5)	[b]

[a] $p<0.02$ eu- versus hyperthyroid patients
[b] $p<0.03$ eu- versus hyperthyroid patients

The thyroid weight was similar in both groups of patients. The 24-h thyroid radioactive iodide uptake was significantly lower in euthyroid patients ($p < 0.02$). The total administered activity was higher in euthyroid than in hyperthyroid patients, although the difference was not significant. No significant differences in cumulated absorbed doses between eu- and hyperthyroid patients were observed at any of the three locations on the skin.

Cumulated absorbed doses at all three locations were significantly correlated with the total activity retained in the thyroid at 24 hours (administered activity × 24-h RAIU) ($r = 0.64$, $p^{**} < 0.001$ for the thyroid location; $r = 0.70$, $p^{**} < 0.001$ for the submandibular location; $r = 0.58$, $p^{**} < 0.005$ for the parotid location). The correlation between absorbed doses on the skin over the salivary glands and the total activity retained in the thyroid at 24 hours divided by the distance of these locations from the ipsilateral top of the thyroid gland was even higher (administered activity × 24-h RAIU / distance) ($r = 0.80$, $p^{**} < 0.001$ for the submandibular location and $r = 0.68$, $p^{**} < 0.003$ for the parotid location). The correlation of the cumulated absorbed dose on the skin with the total administered activity was only significant for the location over the thyroid gland ($r = 0.56$, $p^{**} < 0.01$) and no correlation of cumulated absorbed doses on the skin with 24-h RAIU was found ($p^{**} > 0.1$). The effective half-time of ^{131}I in the thyroid gland, as measured by TLDs, was significantly higher for euthyroid patients (6.1 ± 0.8 days) than for hyperthyroid patients (5.5 ± 0.7 days; $p^{**} < 0.03$).

Thyroid radioactivity measurements; dosimetric calculations; risk estimates

Table 8.2 shows patient characteristics and data of thyroid radioactivity measurements in 6 eu- and 6 hyperthyroid patients. The thyroid weight was similar for eu- and hyperthyroid patients.

There were no significant differences in administered activity, 24-h RAIU or effective half-time of ^{131}I in the thyroid (thyroid radioactivity measurements) between both groups. Residence times in source organs, as calculated from thyroid radioactivity measurements and the aforementioned biokinetic model [5] with modifications [10, 11], did not differ significantly between eu- and hyperthyroid patients, except for the residence time in the liver, which was significantly higher for hyperthyroid patients ($p^{**} < 0.03$) (Table 8.2). Effective half times of ^{131}I in the thyroid resulting from thyroid radioactivity measurements were not significantly different from those measured with TLDs in the same 12 patients (Wilcoxon sign-rank test, $p^{*} = 0.7$). Moreover, a highly significant correlation was found between the cumulated activity (in MBq·h) in the thyroid and the cumulated absorbed dose on the skin overlying the thyroid as measured with TLDs in the same 12 patients ($r = 0.75$, $p^{**} < 0.01$).

Table 8.2 *Patient characteristics and data of thyroid radioactivity measurements after radioiodine treatment of euthyroid and hyperthyroid patients with a large multinodular goiter (>100 g). The mean values ± SD are given (in parentheses ranges are given)*

	Euthyroid		Hyperthyroid		
Number of patients	6		6		
Age (years)	65 ± 10	(52–81)	70 ± 6	(63–80)	
Female : male ratio	5 : 1		3 : 3		
Thyroid weight (g)	203 ± 84	(126–351)	206 ± 59	(130–274)	
24-h RAIU tracer activity (%)	37 ± 11	(21–48)	51 ± 11	(35–63)	[a]
24-h RAIU therapeutic activity (%)	37 ± 16	(17–58)	52 ± 5	(47–59)	[a]
Therapeutic activity of ^{131}I (GBq)	2.2 ± 1.1	(1.2–4.0)	1.6 ± 0.6	(0.8–2.2)	
Effective half-time of ^{131}I in thyroid (d)	5.7 ± 0.4	(5.1–6.1)	5.3 ± 0.5	(4.7–6.1)	
Biological half-time of ^{131}I in thyroid (d)	21 ± 6	(14–31)	18 ± 5	(11–25)	
Cumulated activity thyroid (MBq·h)	160 ± 110	(67–377)	155 ± 57	(82–215)	
Residence time of ^{131}I in					
- thyroid (h) [b]	77 ± 34	(37–120)	99 ± 11	(82–116)	
- stomach (h) [c]	1.23 ± 0.31	(0.84–1.62)	0.96 ± 0.08	(0.82–1.04)	
- small intestine (h) [c]	1.40 ± 0.35	(0.95–1.83)	1.09 ± 0.10	(0.93–1.18)	
- liver (h) [c]	0.70 ± 0.17	(0.47–0.90)	1.00 ± 0.16	(0.71–1.16)	[d]
- rest body (h) [c]	6.3 ± 1.1	(4.9–7.6)	5.5 ± 0.4	(5.0–6.0)	
- urinary bladder (h) [c]	1.5 ± 0.2	(1.2–1.7)	1.3 ± 0.1	(1.2–1.4)	

[a] $p<0.02$ eu- versus hyperthyroid patients

[b] calculated from thyroid radioactivity measurements

[c] calculated using thyroid radioactivity measurements and the biokinetic model of Robertson and Gorman [5] with amendments based on MIRD pamphlet no. 12 [10] and MIRD report no. 5 [11]

[d] $p<0.03$ eu- versus hyperthyroid patients

Table 8.3 shows the calculated absorbed doses in the tissues and organs for which a tissue weighting factor has been determined [6], expressed as dose per unit of administered radioiodine (in mGy/MBq) and as dose resulting from the total administered activities of radioiodine (in Gy). Outside the thyroid gland the highest absorbed doses per MBq of administered ^{131}I were calculated for the urinary bladder, followed by the stomach and small intestine. Inverse correlations were found between the 24-h RAIU and the absorbed doses per MBq in the stomach ($r = -0.97$, $p^{**} < 0.001$), small intestine ($r = -0.98$, $p^{**} < 0.001$) and urinary bladder ($r = -0.85$, $p^{**} < 0.01$). The absorbed dose per MBq in the liver was positively correlated with the 24-h RAIU ($r = 0.83$, $p^{**} < 0.001$). The absorbed dose per MBq in the liver was significantly higher in hyperthyroid than in euthyroid patients ($p^{**} < 0.03$). There were no other significant differences for organ doses per MBq between eu- and hyperthyroid patients.

Extrathyroidal doses resulting from the total administered activities ranged between 0.06 Gy (testes) and 1.06 Gy (urinary bladder) in euthyroid patients and between 0.04 Gy (testes) and 0.71 Gy (urinary bladder) in hyperthyroid patients (average values of six patients in both groups). No significant correlations of absorbed doses (Gy) with 24-h RAIU were found. The mean absorbed doses in most tissues were about similar for eu- and hyperthyroid patients ($p > 0.3$). The mean absorbed doses in stomach, small intestine and urinary bladder were higher for eu- than for hyperthyroid patients. However, these differences were not significant.

The effective dose for the combined organs and tissues outside the thyroid gland was not significantly different for eu- (0.26 ± 0.14 Sv) and hyperthyroid patients (0.19 ± 0.07 Sv). Using the total detriment of 7.3%/Sv given in ICRP Publication 60 [6], the life-time risk of cancer for the combined organs and tissues outside the thyroid can be estimated as $1.8\% \pm 1.0\%$ for euthyroid patients and $1.3\% \pm 0.5\%$ for hyperthyroid patients in the present study (difference eu- versus hyperthyroid not significant). A total detriment of 7.3% / Sv is, however, an average for a population of all ages. For people of 65 years and older the probability of radiation-induced cancer is only about one-fifth of the average [6]. Because 8 of 12 patients in the present study were older than 65 years and only one patient was younger than 60 years an estimate of approximately 0.3% life-time risk of cancer (outside the thyroid gland) seems more appropriate.

Table 8.3 *Radiation absorbed doses in target organs after radioiodine treatment of eu- and hyperthyroid patients with a large multinodular goiter (>100 g) calculated with the MIRD method, using thyroid, urinary bladder, stomach, small intestine, liver and remainder of the body as source organs. The mean values ± SD are given*

Target organ	Absorbed dose per unit administered activity (mGy/MBq)		Absorbed dose (Gy)	
	Euthyroid	Hyperthyroid	Euthyroid	Hyperthyroid
Number of patients	6	6	6	6
Thyroid [a]	46 ± 21	58 ± 17	84 ± 22	83 ± 15
Red bone marrow	0.092 ± 0.024	0.108 ± 0.008	0.19 ± 0.11	0.16 ± 0.08
Ovaries	0.044 ± 0.008	0.039 ± 0.002	0.10 ± 0.06	0.06 ± 0.02
Testes	0.025 ± 0.004	0.023 ± 0.001	0.06 ± 0.03	0.04 ± 0.01
Colon [b]	0.044 ± 0.008	0.038 ± 0.002	0.10 ± 0.06	0.06 ± 0.02
Lung	0.089 ± 0.028	0.107 ± 0.009	0.19 ± 0.11	0.17 ± 0.06
Stomach	0.33 ± 0.08	0.26 ± 0.02	0.74 ± 0.49	0.41 ± 0.16
Urinary bladder	0.48 ± 0.08	0.43 ± 0.03	1.06 ± 0.63	0.71 ± 0.30
Breast	0.045 ± 0.010	0.051 ± 0.003	0.10 ± 0.05	0.08 ± 0.03
Liver	0.078 ± 0.012	0.099 ± 0.011 [c]	0.17 ± 0.08	0.16 ± 0.06
Skin	0.056 ± 0.015	0.066 ± 0.005	0.12 ± 0.07	0.11 ± 0.03
Bone surface	0.116 ± 0.037	0.140 ± 0.013	0.24 ± 0.14	0.22 ± 0.09
Remainder [d]	0.085 ± 0.006	0.088 ± 0.003	0.18 ± 0.09	0.14 ± 0.05
Effective dose outside thyroid (Sv)			0.27 ± 0.14	0.19 ± 0.07

[a] Thyroid absorbed doses as calculated with MIRDOSE2 are corrected for the ratio normal thyroid weight (20 g) / measured actual thyroid weight

[b] 0.57 × dose upper large intestine + 0.43 × dose lower large intestine [6]

[c] $p<0.03$ eu- versus hyperthyroid patients

[d] The absorbed dose in the "remainder of the body" is the average dose in the following organs and tissues: adrenals, brain, upper large intestine, small intestine, kidney, muscle, pancreas, spleen, thymus and uterus [6]

8.4 Discussion

In the present study thermoluminescent dosimeter (TLD) measurements showed cumulated (*i.e.* time-integrated) radiation absorbed doses of 4.2 ± 1.4 Gy on the skin directly overlying the thyroid, of 1.2 ± 0.6 Gy on the skin over the submandibular gland and of 0.4 ± 0.2 Gy on the skin over the parotid gland, after therapeutic administration of ^{131}I in patients with a large, multinodular goiter (mean thyroid weight 222 ± 72 g). There were no significant differences between eu- and hyperthyroid patients. Absorbed doses at all three locations were significantly correlated with the amount of radioiodine retained in the thyroid at 24 hours. Absorbed doses in the spinal cord must have been lower than the doses measured on the skin over the thyroid because the distance between the posterior edge of the thyroid and the spinal cord is considerably larger than the distance between the anterior edge of the thyroid and the surface of the skin. This implies that the cervical spinal cord has absorbed less than one tenth of the dose which in external radiation therapy is considered the threshold dose above which necrosis of the spinal cord may be induced (approximately 55 Gy delivered over 5 to 6 weeks) [13]. On the other hand, it is likely that in a number of our patients the esophageal and tracheal mucosa at the level of the thyroid gland have absorbed higher doses of gamma radiation than those measured with thermoluminescent dosimeters (TLDs) on the skin, because in many patients with a large goiter, thyroid tissue is immediately adjacent to the trachea and esophagus on the anterior as well as on the right and left side. However, it is not to be expected that significant doses of beta radiation have been absorbed in the esophageal and tracheal mucosa, because the maximal range of beta particles of ^{131}I in tissues is 3 mm and the average range only 0.3 mm.

The significant correlation between absorbed doses on the skin overlying the salivary glands on one hand and the amount of radioiodine in the thyroid at 24 hours divided by the distance between the TLDs and the thyroid on the other suggests that these doses were for a large part caused by gamma radiation from radioiodine in the thyroid gland. Absorbed doses within the salivary glands will have been higher than those measured on the skin, because of beta irradiation from inorganic ^{131}I concentrated in these glands. The methods we used do not permit further quantification of the absorbed doses within the salivary glands.

Our TLD measurements in 23 patients showed a small but significant difference in effective half-times of ^{131}I in the thyroid between eu- and hyperthyroid patients (6.1 ± 0.8 days and 5.5 ± 0.7 days, respectively). Thyroid radioactivity measurements with a NaI detector in 12 patients showed similar effective half-times of ^{131}I in the thyroid. Using this method the difference between eu- and

hyperthyroid patients was not significant (5.7 ± 0.4 days and 5.3 ± 0.5 days, respectively). The effective half-time of approximately 5.5 days for hyperthyroid patients found in our study is comparable to other reports on hyperthyroid patients [14–17]. However, the observed effective half-times in hyperthyroid as well as in euthyroid patients are considerably lower than those reported in the dose estimate reports for radioiodine in ICRP Publication 53 (7.3 days) [18] and MIRD report no. 5 (6.9 days) [11] which apply to tracer doses of ^{131}I in euthyroid adults. The fast release of ^{131}I from the thyroid found in our study is probably caused by radiation-induced damage to thyroid cells from therapeutic activities of radioiodine [5, 17, 19, 20]. In view of the small difference between eu- and hyperthyroid patients, the elimination rate of therapeutic activities of radioiodine from the thyroid appears to be less dependent on the functional state of the thyroid at the time of therapy.

A highly significant correlation between the cumulated dose on the skin overlying the thyroid and the cumulated activity within the thyroid as measured with a NaI detector was found. However, TLD measurements depend too much on thyroid mass, depth and geometry to warrant their use in estimating absorbed doses within the thyroid [21]. Therefore, we used radioactivity measurements with a NaI detector to estimate absorbed doses in the thyroid. The absorbed dose in the thyroid of approximately 85 Gy for both eu- and hyperthyroid patients, found in our study, is in the lower range of doses commonly used for the treatment of toxic multinodular goiter (80–200 Gy) [22–25]. This is explained by the combination of a relatively low administered activity per gram of thyroid tissue and a short effective half-time in the thyroid. Uncertainty in our calculations of thyroid absorbed doses is caused by the inaccuracy of thyroid weight estimations by planar scintigraphy [26, 27]. Furthermore, the calculated absorbed dose in the thyroid is an average value for the whole thyroid gland. In a nodular goiter, considerable regional differences in absorbed doses are caused by inhomogeneous radioiodine uptake within the goiter.

Using radioactivity measurements and the biokinetic model of Robertson and Gorman [5], the mean values for absorbed doses in extrathyroidal tissues and organs ranged from 0.024 to 0.46 mGy/MBq of administered radioiodine. Absorbed doses per MBq in the urinary bladder, stomach and small intestine were inversely correlated with 24-h RAIU, because a larger uptake of inorganic iodide into the thyroid gland reduces the residence time of inorganic ^{131}I in the urinary bladder and other extrathyroidal organs. The liver, unlike stomach, small intestine and urinary bladder, is the organ where ^{131}I incorporated in thyroid hormones is collected and metabolized. This was accounted for by assigning 40% of the extrathyroidal thyroid hormone compartment to the liver [10, 11]. This

explains why the absorbed dose per MBq in the liver was positively correlated with the 24-h RAIU, which is an indicator of the synthesis of thyroid hormones. However, for the absorbed doses resulting from the total administered activities of radioiodine no significant correlations with the 24-h RAIU were found, probably because the administered activities depended for an important part on the thyroid weight.

The absorbed doses per MBq of administered ^{131}I found in our study are in accordance with data in the literature, obtained by other techniques of measurement and other biokinetic models [11, 18, 28–30]. However, our patients with large, multinodular goiters and a low thyroid radioiodide uptake received considerably larger total activities of radioiodine than the amounts that are commonly used in patients with Graves' disease. Therefore, extrathyroidal radiation absorbed doses (in Gy) were about four times as high as those reported for patients with Graves' disease in the literature [5, 31–34].

The risk of induction of thyroid cancer by external radiation is dose-dependent [35]. Absorbed doses in the thyroid during radioiodine therapy are more than 10 times as high as doses reported for external irradiation. However, in studies with a long-term follow-up of large numbers of patients treated with radioiodine for hyperthyroidism no significantly increased risk of thyroid cancer was found [33, 34, 36, 37]. It has been suggested that high doses, as absorbed in the thyroid during radioiodine therapy for hyperthyroidism, lead to substantial cell killing and cell sterilization instead of the production of carcinogenic mutations in the cell's DNA [33, 35, 38]. Although our patients with large goiters received higher total amounts of radioiodine than the patients in the aforementioned follow-up studies [33, 34, 36, 37] absorbed doses in the thyroid were similar. Therefore, an elevated risk of thyroid cancer is not to be expected in these patients with a large goiter.

From studies with follow-up up to 35 years, there is no evidence that the overall cancer incidence and cancer mortality in patients with Graves' disease treated with radioiodine are elevated [33, 34, 39, 40]. Literature on cancer incidences after radioiodine therapy relating specifically to patients with nodular goiter is sparse. In one study, a slightly elevated overall cancer incidence was reported in patients with toxic nodular goiter treated with radioiodine (average administered activity 700 MBq), possibly related to higher administered activities than those administered to patients with Graves' disease (average administered activity 360 MBq) [33]. This remains to be confirmed in other studies. With respect to the incidence of cancers of individual extrathyroidal organs and tissues in patients treated with radioiodine for hyperthyroidism (Graves' disease or nodular goiter), the risk of leukemia appears not to be elevated [41–43]. The

risk of cancer of the stomach may be slightly increased [33, 34]. In some studies, the incidences of bladder cancer and of breast cancer have been reported to be increased [42, 44, 45]. However, these findings have not been confirmed by other studies [33, 34, 42].

In our study, patients with a large, multinodular goiter were treated with considerably larger amounts of radioiodine (2000 MBq on average) than the average doses administered in the aforementioned studies. Using a total detriment of 7.3%/Sv for a population of all ages [6], we calculated a 1.6% life-time risk of (fatal and non-fatal) cancer for the combined organs outside the thyroid. When applied to people over 65 years of age, the estimated risk is lower (0.3%). This figure is of the same order of magnitude as that reported for the surgical mortality of subtotal thyroidectomy [1, 3]. The risks of surgery are of course higher in elderly patients, in patients with a large goiter and in those with cardiopulmonary disease [2]. Furthermore, the morbidity of thyroid surgery, including non-fatal complications, is considerably larger [1–3]. However, it has to be stressed that the calculated risk of radioiodine therapy is only a rough estimate of risk and that no follow-up data on cancer incidence in patients with a large goiter treated with high doses of radioiodine are available.

In conclusion, the estimated risks of both surgery and radioiodine should be carefully weighed in all patients with a large, multinodular goiter who have to be treated for hyperthyroidism or compressive problems. In younger patients surgery may be preferred, especially when the amount of radioiodine to be administered, as calculated from a radioiodine tracer study, is high. However, for elderly patients and patients with cardiopulmonary disease, the profits of non-invasive radioiodine treatment will outweigh the life-time risk of this mode of therapy.

8.5 Appendix

Cumulated fractional activities (*i.e.* residence times) in the 4 compartments (B, T, P, and U) are expressed as follows:

(1) $\tilde{B}(0,\infty) = \frac{1}{\lambda+r_1+r_2}$

(2) $\tilde{T}(0,\infty) = \frac{r_1}{r_1+r_2}\{\tilde{I}(0,24) - \tilde{B}(0,24)\} + \frac{1}{\lambda+r_3}\{\frac{r_2 B(24)}{\lambda+r_1+r_2} + T(24)\}$

(3) $\tilde{P}(24,\infty) = \frac{r_3}{\lambda+r_1}\tilde{T}(24,\infty)$

(4) $\tilde{U}(0,\infty) = \frac{r_1}{r_2}\tilde{T}(0,24) + \frac{1}{\lambda}\{r_1[\tilde{B}(24,\infty) + \tilde{P}(24,\infty)] + U(24)\}$

where $\tilde{I}(0,24) = \frac{1}{\lambda}(1 - e^{-24\lambda})$ and where it is assumed that $B_0 = 1$ and $T_0 = U_0 = P_0 = 0$

(5) $T(24) = T_F(1 - e^{-24(r_1+r_2)})$

where T_F is the final or theoretical maximal thyroid ^{131}I uptake.

Acknowledgments

The authors thank Mr. A. de Leeuw for technical assistance.

8.6 References

1 Studley JGN, Lynn J. Surgical anatomy of the thyroid gland and the technique of thyroidectomy. *In: Lynn J, Bloom SR, eds. Surgical Endocrinology. Oxford: Butterworth-Heinemann* 1993:231–40

2 Weitensfelder W, Lexer G, Aigner H, Fellinger H, Trattnig J, Grünbacher G. Die langfristige laryngoskopische Nachkontrolle bei Einschränkung der Stimmbandmotilität nach Strumaoperation. *Chirurg* 1989;60:29-32

3 Foster RS. Morbidity and mortality after thyroidectomy. *Surg Gynecol Obstet* 1978;146:423–9

4 Huysmans DAKC, Hermus ARMM, Barentsz JO, Corstens FHM, Kloppenborg PWC. Large, compressive goiters treated with radioiodine. *Ann Intern Med* 1994; 121:757–62

5 Robertson JS, Gorman CA. Gonadal radiation dose and its genetic significance in radioiodine therapy of hyperthyroidism. *J Nucl Med* 1976;17:826–35

6 1990 Recommendations of the International Commission on Radiological Protection. *ICRP Publication 60. Oxford: Pergamon* 1991

7 Doering P, Kramer K. Die Bestimmung des Schilddrüsengewichtes mit der Szintigraphie nach Gabe von Radiojod; Ein Beitrag zur Dosierung des Radioisotopes. *Strahlenther* 1958;105:245–59

8 DeGroot LJ. Graves' disease diagnosis and treatment. Multinodular goitre. *In: DeGroot LJ, Stanbury JB, eds. The Thyroid and Its Diseases, 4th ed. New York: Wiley* 1975:314–67 and 637–65

9 Keating FR, Power MH, Berkson J, *et al.* The urinary excretion of radioiodine in various thyroid states. *J Clin Invest* 1947;26:1138–51

10 Berman M. Kinetic Models for Absorbed Dose Calculations; Appendix B. Iodine kinetics. *In: Cloutier RJ, Smith EM, eds. MIRD Pamphlet No. 12. New York: Society of Nuclear Medicine* 1977:11–3

11 Berman M, Braverman LE, Burke J, DeGroot L, McCormack KR, Oddie TH, Rohrer RH, Wellman HN, Smith EM. MIRD dose estimate report no. 5: Summary of current radiation dose estimates to humans from ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{130}I, ^{131}I, and ^{132}I as sodium iodide. *J Nucl Med* 1975;16:857–60

12 Loevinger R, Berman M. A revised scheme for calculating the absorbed dose from biologically distributed radionuclides. *MIRD Pamphlet No. 1, revised. New York: Society of Nuclear Medicine* 1975

13 Misadministrations of radioactive material in medicine. Scientific background. *NCRP Commentary No. 7. Bethesda: NCRP* 1991

14 DeGroot LJ. Kinetic analysis of iodine metabolism. *J Clin Endocr* 1966;26:149-73

15 Werner SC, Johnson PM, Goodwin PM, Wiener JD, Linderboom GA. Long-term results with iodine-125 treatment for toxic diffuse goitre. *Lancet* 1970;ii:681–5

16 Müller B, Bares R, Büll U. Untersuchungen zur effektiven Halbwertzeit des ^{131}J bei der Radiojodbehandlung der Schilddrüsenautonomie. *Nuklearmedizin* 1991; 30:71–6

17 Bockisch A, Jamitzky T, Derwanz R, Biersack HJ. Optimized dose planning of radioiodine therapy of benign thyroidal diseases. *J Nucl Med* 1993;34:1632–8

18 Radiation Dose to Patients from Radiopharmaceuticals; Iodide ^{123}I, ^{124}I, ^{125}I, ^{131}I. *In: ICRP Publication 53. New York: Pergamon* 1987:259–78

19 Freedberg AS, Kurland GS, Chamovitz DL, Ureles AL. Critical analysis of I-131 therapy. *J Clin Endocr* 1952;12:86–111

20 Joyet G, Miller M. Essai de dosage rationnel du traitement radio-actif des hyperthyréoses par l' ^{131}I: méthode de dosage et résultats statistiques. *Ann Radiol* 1962; 5:21–44

21 O'Connor MK, Cullen MJ, Malone JF. The influence of thyroid geometry on the response of LiF and CaSo4 thermoluminescent discs to ^{131}I and ^{125}I irradiation. *Phys Med Biol* 1978;23:712–22

22 Glanzmann Ch, Kaestner F, Horst W. Therapie der Hyperthyreose mit Radio-Isotopen des Jods: Erfahrungen bei über 2000 Patienten. *Klin Wochenschr* 1975; 53:669–78

23 Holm LE, Lundell G, Israelsson A, Dahlqvist I. Incidence of hypothyroidism occurring long after iodine-131 therapy for hyperthyroidism. *J Nucl Med* 1982;23:103–7

24 Hoeschel M, Heinze HG. 131-J-Therapie des Morbus Basedow und der nicht-immunogenen Hyperthyreose. *Nuklearmedizin* 1984;23:143–9

25 Berding G, Schicha H. Ergebnisse der Radiojodtherapie der manifesten Hyperthyreose und der autonomen Struma mit Euthyreose. *Nuklearmedizin* 1990;29:158–65

26 Fazakas S, Balázs G, Petrányi G, Szeleczky G. Zur Bestimmung des Schilddrüsengewichtes mittels einer szintigraphischen Methode. *Nuklearmedizin* 1964;4:56–62

27 Brown MC, Spencer R. Thyroid gland volume estimated by use of ultrasound in addition to scintigraphy. *Acta Radiol Oncol* 1978;17:337–41

28 Philippon B, Briere J. Absorbed dose to ovaries and uterus during ^{131}I-treatment of hyperthyroidism: comparison between *in vivo* TLD measurements and calculations. *Health Phys* 1979;36:727–9

29 McEwan AC. Absorbed doses in the marrow during ^{131}I therapy. *Br J Radiol* 1977; 50:329–31

30 Stabin MG, Watson EE, Marcus CS, Salk RD. Radiation dosimetry for the adult female and fetus from iodine-131 administration in hyperthyroidism. *J Nucl Med* 1991;32:808–13

31 Halnan KE. Risks from radioiodine treatment of thyrotoxicosis. *Br Med J* 1983; 287:1821–2

32 Graham GD, Burman KD. Radioiodine treatment of Graves' disease; an assessment of its potential risks. *Ann Intern Med* 1986;105:900–5

33 Holm LE, Hall P, Wiklund K, Lundell G, Berg G, Bjelkengren G, *et al.* Cancer risk after iodine-131 therapy for hyperthyroidism. *J Natl Cancer Inst* 1991;83:1072–7

34 Hall P, Berg G, Bjelkengren G, Boice JD, Ericsson UB, Hallquist A, *et al.* Cancer mortality after iodine-131 therapy for hyperthyroidism. *Int J Cancer* 1992;50:886–90

35 Shore RE. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. *Radiat Res* 1992;131:98–111

36 Van Middlesworth L. Effects of radiation on the thyroid gland. *In: Siperstein MD, ed. Advances in Internal Medicine, No 34. Year Book Medical Publishers* 1989:265–84

37 Dobyns BM, Sheline GE, Workman JB, Tompkins EA, McConahey WM, Becker DV. Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the Cooperative Thryotoxicosis Therapy Follow-up Study. *J Clin Endocrinol Metab* 1974;38:976–98

38 Holm LE, Dahlqvist I, Israelsson A, Lundell G. Malignant thyroid tumors after iodine-131 therapy; a retrospective cohort study. *N Engl J Med* 1980;303:188–91

39 Hoffman DA. Late effects of I-131 therapy in the United States. *In: Boice JD, Fraumeni JR, eds. Progress in cancer research and therapy. Radiation carcinogenesis: epidemiology and biological significance; Vol 26. New York: Raven* 1984:273–80

40 Hennemann G, Krenning EP, Sankaranarayanan K. Place of radioactive iodine in treatment of thyrotoxicosis. *Lancet* 1986;i:1369–72

41 Saenger EL, Thoma GE, Tompkins EA. Incidence of leukemia following treatment of hyperthyroidism. *JAMA* 1968;205:855–62

42 Hoffman DA, McConahey WM, Fraumeni JF, Kurland LT. Cancer incidence following treatment of hyperthyroidism. *Int J Epidemiol* 1982;11:218–24

43 Hall P, Boice JD, Berg G, Bjelkengren G, Ericsson UB, Hallquist A, *et al.* Leukaemia incidence after iodine-131 exposure. *Lancet* 1992;340:1–4

44 Hoffman DA, McConahey WM. Breast cancer following iodine-131 therapy for hyperthyroidism. *J Natl Cancer Inst* 1983;70:63–7

45 Goldman MB, Maloof F, Monson RR et al. Radioactive iodine therapy and breast cancer: a follow-up study of hyperthyroid women. *Am J Epidemiol* 1988;127:969–80

Summary

Multinodular goiter is defined as a structurally and functionally heterogeneous thyroid enlargement. It arises from excessive replication of thyroid epithelial cells with subsequent generation of new follicles of widely differing structure and function. The size of such a goiter tends to increase with age and, although the thyroid may be diffusely enlarged in the first phase of goitrogenesis, it will become more nodular with time. Moreover, euthyroidism may gradually change into hyperthyroidism in patients with a multinodular goiter.

A **solitary autonomous thyroid nodule** is a discrete thyroid nodule that secretes thyroid hormone, independently of any known extrathyroidal stimulus. It may exist in close approximation to and within normal thyroid parenchyma that remains subject to the functional regulation of the pituitary. As a solitary autonomous thyroid nodule is generated from follicular cells with (most probably) genetically determined high replication rate and iodinating capacity, its size tends to increase with time, not infrequently leading to hyperthyroidism.

Results of radioiodine therapy in patients with Graves' disease have been evaluated extensively. Considerably less has been reported on results of radioiodine treatment in patients with a uni- or multinodular goiter. This thesis is focused on various aspects of radioiodine therapy in such patients. Three groups of patients were studied: patients with a toxic solitary autonomous thyroid nodule (chapters 2 and 3), those with a toxic multinodular goiter (chapters 4 and 5) and those with a compressive, toxic or non-toxic, multinodular goiter (chapters 6, 7 and 8). Long-term effects of radioiodine treatment on thyroid function in patients with a toxic solitary autonomous thyroid nodule are evaluated in chapter 3. In chapter 4 and 5 long-term effects of radioiodine treatment on thyroid function in patients with a toxic multinodular goiter are described. The effectiveness of radioiodine therapy to reduce thyroid volume and to reverse compression of vital structures in patients with a large, compressive, multinodular goiter is studied in chapter 7, while dosimetric aspects of radioiodine treatment in this group of patients are discussed in chapter 8. Chapters 2 and 6 contain studies evaluating the value of imaging procedures in patients with a nodular goiter. In chapter 2, thallium-201 scintigraphy and iodine-123 scintigraphy after stimulation with thyroid-stimulating hormone (TSH) for the visualization of suppressed extranodular thyroid tissue in patients with a toxic solitary autonomous thyroid nodule are compared. Chapter 6 contains a comparison of thyroid volume measurements with magnetic resonance imaging (MRI) and those obtained with planar scintigraphy in patients with a large, multinodular goiter.

In **chapter 1**, preceding the original studies, a review of current knowledge of the pathogenesis and natural history of multinodular goiter and toxic

solitary autonomous thyroid nodules and a summary of cell biological effects of radioiodine on the thyroid gland are given.

In **chapter 2** the use of thallium-201 (^{201}Tl) scintigraphy for the visualization of suppressed extranodular thyroid tissue is evaluated in 21 patients with a toxic solitary autonomous thyroid nodule. ^{201}Tl scintigraphy is compared with I-123 (^{123}I) scintigraphy after stimulation with bovine TSH. In all patients similar results were obtained with both methods. The contralateral lobe of the thyroid was visualized in 20 patients and the extranodular part of the ipsilateral lobe in 14 of these patients, on both ^{201}Tl scintigraphy and TSH stimulated ^{123}I scintigraphy. In one patient no extranodular thyroid tissue was shown with either method. It is concluded that ^{201}Tl scintigraphy is a reliable and simple alternative for TSH stimulated ^{123}I scintigraphy for the visualization of suppressed extranodular thyroid tissue in patients with a toxic solitary autonomous thyroid nodule. ^{201}Tl does not induce allergic reactions, which are frequently seen after injections of bovine TSH. Iodide uptake in extranodular tissue is not stimulated by ^{201}Tl and therefore, ^{201}Tl scintigraphy and radioiodine therapy can be combined on one day, without increasing the risk of post-treatment hypothyroidism due to radiation-induced damage of normal thyroid tissue.

In **chapter 3** the long-term effects of radioiodine treatment on thyroid function in patients with a toxic solitary autonomous thyroid nodule are evaluated. Fifty-two patients treated with a therapeutic dose of 740 MBq (20 mCi) of ^{131}I in the past were examined after a follow-up of 10 ± 4 (mean $\pm$ SD) years. All patients had become euthyroid within six months after radioiodine therapy. In one patient (2%) hyperthyroidism had recurred after 1.5 years, which was successfully treated with a second dose of 740 MBq of radioiodine. At the end of follow-up, hypothyroidism was present in 6% of patients. It is concluded that a standard dose of 740 MBq of radioiodine is a highly effective treatment for patients with a toxic solitary autonomous thyroid nodule. The risk of development of hypothyroidism is low if extranodular uptake of ^{131}I is minimized. This will be achieved when radioiodine treatment is only given when the serum TSH level is suppressed.

In **chapter 4** the long-term effects of two schedules of radioiodine therapy in patients with toxic multinodular goiter were evaluated. Forty-five patients (group A) were treated with fixed low doses and fifty-eight patients (group B) with calculated doses adjusted for thyroid weight (1.85–3.70 MBq/g) and radioactive iodide uptake. Follow-up (mean $\pm$ SD) was 4.3 ± 1.3 yr and 5.2 ± 2.3 yr, respectively ($p > 0.1$). At the end of follow-up, hyperthyroidism was successfully reversed in 73% (group A) and 88% (group B). In either group, hypothyroidism was present in 7%. The total dose per gram of thyroid tissue was not significantly different in groups A and B (2.1 ± 1.5 versus 2.7 ± 1.3 MBq/g). However,

for patients treated with calculated doses the number of ^{131}I administrations was significantly lower (1.3 ± 0.8) than for patients treated with low doses (2.2 ± 1.3) and the percentage of patients who were adequately treated with a single dose was more than twice as high (66% in group B versus 27% in group A). Euthyroidism was reached within a significantly shorter time after treatment with calculated doses (median time 0.6 years in group B versus 1.5 years in group A; life table analysis). It is concluded that radioiodine is an effective treatment for toxic multinodular goiter with a low risk of post-treatment hypothyroidism and that calculated (higher) doses appear to be preferable to low doses.

In **chapter 5** a follow-up study is presented of patients, who were euthyroid at the end of the study presented in chapter four, 1 to 12 years after radioiodine treatment for toxic multinodular goiter. There were two reasons to perform such a follow-up study. First, we observed significant inverse correlations between serum fT_4 and T_3 levels on one hand and serum TSH levels on the other in the 71 euthyroid patients of groups A and B at the end of the study reported in chapter four. Second, 30% of the euthyroid patients had a serum TSH level below the normal range at that time. These observations suggest that, in spite of normal serum levels of fT_4 and T_3, autonomous thyroid function is still present in (a number of) these radioiodine treated patients and that they are at risk of recurrent hyperthyroidism. Forty-nine of these euthyroid patients were reexamined 1 year later (February 1993). A subgroup of patients of group B, those who were rendered euthyroid after a single dose of radioiodine in the past, were also evaluated in February 1994 (group B select; n = 21). Our follow-up data demonstrated significant decreases of serum fT_4 and T_3 levels and a significant increase in serum TSH levels after 1 year. In the majority of patients, fT_4 levels had decreased (34 of 49 patients) or stayed at the same level (3 of 49 patients) after one year. Even in 13 of 18 patients, who had a TSH value below the normal range in 1992, fT_4 levels had decreased 1 year later. Significant decreases in serum fT_4 and T_3 levels were also observed between February 1992 and February 1994 in group B select. In 19 of the 21 patients of group B select fT_4 levels in 1994 were lower than in 1992. On the other hand, in 12 patients of the whole group of 49 euthyroid patients and in 3 of the subgroup of 18 patients with a TSH level below normal in 1992, fT_4 levels had increased after 1 year. An increase to fT_4 levels just above the normal range was seen in only 3 of all 49 euthyroid patients. It is concluded that in patients who have been treated with radioiodine for toxic multinodular goiter in the past and who have fT_4 and T_3 levels within the normal range, a further decrease of thyroid hormone levels can be anticipated, at least in the first decade after radioiodine therapy. This applies even for the subgroup of patients with a serum TSH level below the normal range. Therefore, in these patients an expectative policy with yearly control

visits is indicated. Additional ^{131}I treatment has to be considered in patients with a serum TSH level below the normal range, when serial measurements show a further decrease in TSH levels (or TSH levels below the detection limit of the assay) in combination with increasing fT_4 and T_3 levels, especially when signs and symptoms of thyrotoxicosis recur.

In **chapter 6** the use of magnetic resonance imaging (MRI) for volume estimations of large multinodular goiters is evaluated, in view of a currently growing interest in non-surgical treatment to reduce goiter size. Twenty patients (3 men and 17 women, age 61 ± 21 years; mean $\pm$ SD) with a multinodular goiter larger than 100 ml were studied. In addition, MRI measurements were compared to scintigraphic volume estimations. Intraobserver CV of MRI measurements was $2.2\% \pm 2.0\%$ (observer 1) and interobserver CV $4.1\% \pm 2.2\%$ (observers 1 and 2). In all 20 patients signs of mechanical complications were shown on MRI images. For scintigraphic measurements intraobserver CV was $7.5\% \pm 5.7\%$ (observer 3) and $5.4\% \pm 5.1\%$ (observer 4). Interobserver CV was $10.1\% \pm 6.1\%$. The correlation between measurements with both methods was not strong ($r = 0.665$) and the resulting CV was $17.3\% \pm 14.2\%$. Underestimation of scintigraphic volumes could not be explained by the presence of cysts at the surface of the thyroid. It is concluded that magnetic resonance imaging can be used for *in vivo* thyroid volume estimation of large multinodular goiters. The high precision of MRI measurements makes this technique potentially useful for the evaluation of thyroid growth and non-surgical treatment to reduce goiter size. Scintigraphic volume measurements do not suffice for this purpose. An additional advantage of MRI is the detailed anatomical information it provides on mechanical complications of large goiters.

In **chapter 7** the effectiveness of radioiodine treatment as an alternative for surgery is evaluated prospectively in 19 patients, aged 66 ± 14 years (mean $\pm$ SD) with a large, compressive multinodular goiter (>100 ml), who had a high operative risk or refused to undergo thyroid surgery. A single i.v. dose of 2.6 ± 1.0 GBq (70 ± 28 mCi) of ^{131}I (3.7 MBq or 100 μCi per gram of thyroid tissue) was administered, followed by daily administration of L-thyroxine in non TSH-suppressive doses. Clinical evaluation and MRI measurements of thyroid volume, maximal tracheal deviation from the midline and the smallest cross-sectional area of the tracheal lumen were performed before and 1 year after radioiodine treatment. Exacerbation of compressive symptoms after ^{131}I was not observed. Before treatment thyroid volume was 269 ± 153 ml and 1 year after radioiodine therapy 154 ± 73 ml ($p < 0.001$). Thyroid volume reduction was $40\% \pm 15\%$ (range, 19% to 68%). Maximal tracheal deviation (1.9 ± 0.8 cm before and 1.5 ± 0.7 cm one year after therapy) had decreased by $20\% \pm 20\%$

(−4% to 73%; $p < 0.001$) and the smallest cross-sectional area of the tracheal lumen (0.78 ± 0.38 cm^2 before and 1.04 ± 0.48 cm^2 1 year after therapy) had increased by $3\% \pm 38\%$ (−3% to 125%; $p < 0.001$). Clinical signs and symptoms had improved in 8 of 12 patients with dyspnea and inspiratory stridor and in both patients with compression of the superior vena cava. It is concluded that radioiodine therapy is an effective alternative for surgery in elderly patients with a large, compressive multinodular goiter.

In **chapter 8** dosimetric aspects of radioiodine therapy in patients with a large, multinodular goiter are studied. Many commonly used dosage schedules for radioiodine therapy are aimed at delivering a certain amount of radioiodine per gram of thyroid tissue retained at 24 hours. The use of such a dosage schedule implies that high doses of radioiodine are administered to patients with a large, multinodular goiter. We estimated absorbed doses in the thyroid, surrounding tissues and rest of the body after therapeutic administration of radioiodine (3.7 MBq/g of thyroid tissue retained at 24 hours) in patients with a large, toxic or non-toxic, multinodular goiter (>100g). Thermoluminescent dosimeter (TLD) measurements on the skin over the thyroid, over the submandibular gland and over the parotid gland were used to estimate the radiation burden of neighbouring tissues due to radioactive iodine in the thyroid gland. TLD measurements in 23 patients (12 eu- and 11 hyperthyroid; thyroid weight 222 ± 72 g, mean ± SD; administered activity 2.1 ± 0.9 GBq) showed cumulated (*i.e.* time-integrated) radiation absorbed doses of 4.2 ± 1.4 gray (Gy) on the skin directly overlying the thyroid, of 1.2 ± 0.6 Gy on the skin over the submandibular gland and of 0.4 ± 0.2 Gy on the skin over the parotid gland. There were no significant differences between eu- and hyperthyroid patients. Absorbed doses at all three locations were significantly correlated with the total amount of radioiodine retained in the thyroid at 24 hours. In 12 patients (6 eu- and 6 hyperthyroid; thyroid weight 204 ± 69 g; administered activity 1.9 ± 0.9 GBq) estimations of thyroid and total-body irradiation were made using thyroid radioactivity measurements and the model of iodine kinetics in the body described by Robertson and Gorman. Absorbed doses in the thyroid were 84 ± 22 Gy for euthyroid and 83 ± 15 Gy for hyperthyroid patients. The highest absorbed doses outside the thyroid were observed for the stomach, the small intestine and the urinary bladder (mean values of 12 patients, 0.38 Gy, 0.57 Gy and 0.88 Gy, respectively). Absorbed doses in all other extrathyroidal tissues were lower and ranged between 0.05 and 0.30 Gy (mean values of 12 patients). There were no significant differences in absorbed doses between eu- and hyperthyroid patients. Absorbed doses in extrathyroidal tissues were about four times as high as those reported for patients with Graves' disease in the literature. The effective dose, which

was primarily determined by the absorbed dose in the thyroid, was similar for eu- and hyperthyroid patients (4.5 ± 1.1 and 4.4 ± 0.8 sievert, respectively). Using official risk estimates [ICRP Publication 60] for a population of all ages, a 1.6% life-time risk of development of cancer outside the thyroid gland was calculated. When applied to people of 65 years and older the estimated risk is lower (about 0.3%). However, it has to be stressed that these data are only rough estimates of risk and that no real follow-up data on cancer incidence in patients with a large, multinodular goiter treated with high doses of radioiodine are available. It is concluded that in all patients with a large, multinodular goiter, who have to be treated for hyperthyroidism or compressive problems, the estimated risks of both surgery and radioiodine should be carefully weighed. In younger patients surgery may be preferred, especially when the amount of radioiodine to be administered as calculated from a radioiodine tracer study is high. However, for elderly patients and patients with cardiopulmonary disease, the profits of non-invasive radioiodine treatment will outweigh the life-time risk of this mode of therapy. For these patients radioiodine therapy seems preferable to surgery.

Samenvatting

Onder een **multinodulaire struma** wordt een, qua structuur en functie, heterogene schildkliervergroting verstaan. Zulk een schildkliervergroting ontstaat door een versnelde deling van schildklierepitheelcellen met als gevolg de vorming van nieuwe schildklierfollikels die in structuur en functie sterk variëren. De grootte van een multinodulaire struma neemt toe met de leeftijd. Hoewel de schildklier in het begin diffuus vergroot kan zijn, zal deze op den duur steeds meer nodulair worden. Bij patiënten met een multinodulaire struma kan een normale schildklierwerking (euthyreoidie) geleidelijk overgaan in een versnelde schildklierwerking (hyperthyreoidie).

Een **solitaire autonome schildkliernodus** is een geïsoleerde nodus in de schildklier die schildklierhormoon produceert, onafhankelijk van stimulatie door thyroid-stimulerend hormoon (TSH) vanuit de hypofyse of enige andere bekende stimulus buiten de schildklier. De nodus is meestal gelegen binnen het normale schildklierweefsel waarvan de functie afhankelijk blijft van regulatie vanuit de hypofyse. Een solitaire autonome schildkliernodus, ontstaand uit follikelcellen met een waarschijnlijk genetisch bepaalde hoge delingssnelheid en hoge joderingscapaciteit, neigt tot groei en leidt niet zelden tot hyperthyreoidie.

Er zijn vele studies gepubliceerd waarin resultaten van behandeling met radioactief jodium bij patiënten met de ziekte van Graves gemeld worden. Er zijn veel minder studies over de resultaten van deze behandeling bij patiënten met een uni- of multinodulaire struma. In dit proefschrift worden verschillende aspecten van behandeling met radioactief jodium bij patiënten met een nodulaire struma bestudeerd. Hierbij worden drie groepen patiënten onderscheiden: patiënten met een solitaire autonome schildkliernodus (hoofdstuk 2 en 3), patiënten met een hyperthyreotische, multinodulaire struma (hoofdstuk 4 en 5) en patiënten met een ongewoon grote, multinodulaire struma, al dan niet met hyperthyreoidie (hoofdstuk 6, 7 en 8).

De effecten op lange termijn van behandeling met radioactief jodium op de schildklierfunctie bij patiënten met een toxische solitaire autonome schildkliernodus worden geëvalueerd in hoofdstuk 3. In hoofdstuk 4 en 5 worden de effecten van behandeling met radioactief jodium op de schildklierfunctie op lange termijn beschreven bij patiënten met een toxische, multinodulaire struma. De resultaten van behandeling met radioactief jodium, gegeven met als doel het volume van de schildklier te verkleinen en compressie van vitale structuren te verminderen bij patiënten met een grote, eu- of hyperthyreotische, multinodulaire struma worden beschreven en becommentariëerd in hoofdstuk 7. In hoofdstuk 8 worden dosimetrische aspecten van therapie met radioactief jodium

bij deze groep van patiënten bediscussiëerd. De hoofdstukken 2 en 6 bevatten studies waarin de waarde van beeldvormende technieken bij patiënten met een nodulaire struma aan de orde wordt gesteld. In hoofdstuk 2 wordt thallium-201 scintigrafie voor de visualisatie van extranodulair schildklierweefsel bij patiënten met een toxische solitaire autonome schildkliernodus vergeleken met jodium-123 scintigrafie na stimulatie met TSH. Hoofdstuk 6 bevat een vergelijking van metingen van schildkliervolumina van grote multinodulaire strumæ, gebruik makend van de magnetische resonantie techniek (MRI) en van planaire scintigrafie.

In **hoofdstuk 1**, voorafgaand aan de studies, wordt een kort overzicht van de huidige kennis van de pathogenese en natuurlijke historie van de multinodulaire struma en de toxische solitaire autonome schildkliernodus en een samenvatting van de celbiologische effecten van radioactief jodium op de schildklier gegeven.

In **hoofdstuk 2** wordt het gebruik van thallium-201 (^{201}Tl) scintigrafie ter visualisering van gesupprimeerd extranodulair schildklierweefsel geëvalueerd bij 21 patiënten met een toxische solitaire autonome schildkliernodus. ^{201}Tl scintigrafie wordt vergeleken met I-123 (^{123}I) scintigrafie na stimulatie met runder-TSH. Met beide methoden werden bij alle patiënten gelijke resultaten verkregen. De contralaterale schildklierkwab werd bij 20 patiënten gevisualiseerd en het extranodulaire deel van de schildklierkwab met de nodus bij 14 van deze patiënten, zowel met ^{201}Tl scintigrafie als met ^{123}I scintigrafie na TSH-stimulatie. Bij één patiënt werd met geen van beide methoden extranodulair schildklierweefsel afgebeeld. Geconcludeerd wordt dat ^{201}Tl scintigrafie een betrouwbaar en simpel alternatief voor ^{123}I scintigrafie na TSH-stimulatie is om bij patiënten met een toxische solitaire autonome schildkliernodus extranodulair schildklierweefsel zichtbaar te maken. ^{201}Tl veroorzaakt geen allergische reacties, die wel frequent gezien werden na injectie van runder-TSH. De opname van radioactief jodium in het extranodulaire weefsel wordt niet gestimuleerd door ^{201}Tl. Daarom kunnen ^{201}Tl scintigrafie en behandeling met radioactief jodium op één dag gecombineerd worden. Het risico van hypothyreoidie door stralingsschade van het normale extranodulaire schildklierweefsel wordt hierdoor niet verhoogd.

In **hoofdstuk 3** worden de effecten op lange termijn van behandeling met radioactief jodium op de schildklierfunctie bij patiënten met een toxische solitaire autonome schildkliernodus geëvalueerd. 52 patiënten, in het verleden behandeld met een standaard therapeutische dosis van 740 MBq (20 mCi) ^{131}I, werden onderzocht na een follow-up van 10 ± 4 jaar (gemiddelde $\pm$ SD). Alle patiënten waren binnen 6 maanden na de behandeling euthyreotisch geworden. Eén patiënt (2%), die na 1.5 jaar opnieuw hyperthyreotisch werd, is met

een tweede dosis van 740 MBq radioactief jodium met succes behandeld. Op het einde van de follow-up was slechts 6% van de patiënten hypothyreotisch. Geconcludeerd wordt dat een standaard dosis van 740 MBq radioactief jodium een zeer effectieve behandeling is voor patiënten met een toxische solitaire autonome schildkliernodus. Het risico van het ontstaan van hypothyreodie is klein wanneer de opname van radioactief jodium in het extranodulaire schildklierweefsel geminimaliseerd wordt. Dit kan bereikt worden door alleen met radioactief jodium te behandelen wanneer de TSH-spiegel in het bloed onderdrukt is.

In **hoofdstuk 4** worden de resultaten op lange termijn van twee schema's van behandeling met radioactief jodium vergeleken bij patiënten met een toxische multinodulaire struma. Vijf en veertig patiënten (groep A) werden behandeld met lage standaarddoses en acht en vijftig patiënten (groep B) met berekende doses waarbij het schildkliergewicht (1.85 tot 3.70 MBq/g) en het percentage opname van radioactief jodium in de schildklier in de berekening meegenomen werden. De follow-up (gemiddelde $\pm$ SD) was respectievelijk 4.3 ± 1.3 jaar en 5.2 ± 2.3 jaar. Op het einde van de follow-up was de hyperthyreoidie in 73% (groep A) en 88% (groep B) met succes bestreden. Hypothyreoidie was aanwezig in 7% van de patiënten in beide groepen. De totale dosis per gram schildklierweefsel verschilde niet significant tussen de groepen A en B (2.1 ± 1.5 versus 2.7 ± 1.3 MBq/g). Wel was bij patiënten behandeld met berekende doses ^{131}I het aantal doseringen (1.3 ± 0.8) significant lager dan bij patiënten behandeld met lage doses (2.2 ± 1.3) en het percentage patiënten dat adequaat was behandeld met één dosering ^{131}I was meer dan twee maal zo hoog in groep B (66% in groep B versus 27% in groep A). Euthyreoidie werd binnen een significant kortere tijd bereikt na behandeling met berekende doses (mediane tijd 0.6 jaar in groep B versus 1.5 jaar in groep A; Kaplan-Meier analyse). Geconcludeerd wordt dat therapie met radioactief jodium een effectieve behandeling is voor patiënten met een toxische multinodulaire struma met een kleine kans op hypothyreoidie na de behandeling. Berekende (hogere) doses zijn te prefereren boven lage doses.

In **hoofdstuk 5** wordt een follow-up studie gepresenteerd van patiënten die aan het einde van de in hoofdstuk 4 beschreven studie, 1 tot 12 jaar na behandeling met radioactief jodium wegens een toxische multinodulaire struma, in leven en euthyreotisch waren. Er waren twee redenen voor deze follow-up studie. Ten eerste namen wij waar, dat de serumspiegels van vrij T_4 en T_3 enerzijds en de serum TSH-spiegels anderzijds, negatief en significant gecorreleerd waren bij de 71 euthyreotische patiënten van groep A en B aan het einde van de studie beschreven in hoofdstuk 4. Voorts had 30% van de euthyreotische patiënten op dat moment een serum TSH-spiegel beneden de ondergrens van normaal. Beide

bevindingen suggereren dat, ondanks de aanwezigheid van normale spiegels van vrij T_4 en T_3 in het serum, de schildklier bij (een aantal van) deze, met radioactief jodium behandelde, patiënten nog steeds autonoom functioneert en dat zij het risico lopen opnieuw hyperthyreotisch te worden. Negen en veertig van deze euthyreotische patiënten werden een jaar later opnieuw onderzocht (in februari 1993). Een subgroep van de patiënten van groep B, diegenen die na één dosis radioactief jodium euthyreotisch geworden waren, werden bovendien in februari 1994 opnieuw onderzocht (groep B_1; n = 21). De follow-up gegevens na 1 jaar lieten significante dalingen van de serumspiegels van vrij T_4 en T_3 zien en een significante stijging van de serum TSH-spiegel. Bij de meerderheid van de patiënten was het vrije T_4 gehalte gedaald (34 van 49 patiënten) of gelijk gebleven (3 van 49 patiënten). Zelfs bij 13 van 18 patiënten die in 1992 een verlaagde TSH-spiegel hadden was het vrije T_4 gehalte een jaar later verder gedaald. Significante dalingen van de serumspiegels van vrij T_4 en T_3 werden ook gezien in groep B_1 tussen februari 1992 en februari 1994. Overigens was de vrije T_4 spiegel niet bij alle patiënten tussen februari 1992 en februari 1993 gedaald. Bij 12 patiënten van de gehele groep van 49 patiënten en bij 3 van de 18 patiënten die in 1992 een verlaagde TSH-spiegel hadden was de vrije T_4 spiegel na een jaar gestegen. Een stijging van de vrije T_4 spiegel tot boven de bovengrens van normaal werd echter slechts bij 3 van de 49 patiënten waargenomen. Geconcludeerd wordt dat bij patiënten, die normale spiegels van vrij T_4 en T_3 in het serum hebben na in het verleden behandeld te zijn met radioactief jodium wegens een toxische multinodulaire struma, een verdere daling van de schildklierhormoongehalten verwacht mag worden, in ieder geval in de eerste decade na de behandeling. Dit geldt ook voor diegenen die een verlaagde serum TSH-spiegel hebben. Bij deze patiënten is een expectatief beleid met jaarlijkse controles geboden. Aanvullende behandeling met radioactief jodium dient overwogen te worden bij patiënten met een verlaagde serum TSH-spiegel wanneer bij volgende controles een verdere daling van de TSH-spiegel (of een TSH-gehalte beneden de detectielimiet van de assay) in combinatie met stijgende vrije T_4 en T_3 gehalten gezien wordt, zeker wanneer ook klachten en verschijnselen van thyreotoxicose terugkeren.

In **hoofdstuk 6** wordt magnetische resonantie (MRI) als techniek voor volumebepaling van grote multinodulaire strumæ geëvalueerd. Dit met het oog op de toenemende belangstelling voor niet-chirurgische behandelingsvormen ter verkleining van strumæ. Twintig patiënten (3 mannen en 17 vrouwen, leeftijd 61 ± 21 jaar;gemiddelde $\pm$ SD) met een multinodulaire struma met een inhoud van meer dan 100 ml werden onderzocht. Bovendien werden MRI-metingen vergeleken met scintigrafische volumemetingen. De intra-observer

variatiecoëfficiënt (CV) van MRI metingen was 2.2% ± 2.0% (onderzoeker 1) en de inter-observer CV 4.2% ± 2.1% (onderzoekers 1 en 2). Bij alle 20 patiënten waren tekenen van mechanische complicaties zichtbaar op de MRI-beelden. Voor scintigrafische metingen waren de verschillen aanzienlijk groter: de intra-observer CV was 7.5% ± 5.7% (onderzoeker 3) en 5.4% ± 5.1% (onderzoeker 4) en de inter-observer CV was 10.1% ± 6.1%. De correlatie tussen MRI metingen en scintigrafische metingen was zwak (r = 0.665) en de resulterende CV was 17.3% ± 14.3%. Onderwaardering van schildkliervolumina door scintigrafie werd niet verklaard door de aanwezigheid van cysten aan het oppervlak van de schildklier. Geconcludeerd wordt dat MRI gebruikt kan worden voor *in vivo* schildkliervolumebepalingen bij grote multinodulaire strumæ. De grote precisie van MRI-metingen maakt deze techniek dan ook goed bruikbaar voor de meting van schildkliergroei en voor evaluatie van niet-chirurgische behandeling van strumæ. Scintigrafische volumebepalingen zijn hiervoor onvoldoende nauwkeurig. Een bijkomend voordeel van MRI is dat gedetailleerde anatomische informatie over mechanische complicaties van grote strumæ verkregen wordt.

In **hoofdstuk 7** wordt de effectiviteit van behandeling met radioactief jodium als alternatief voor schildklierchirurgie op prospectieve wijze geëvalueerd bij 19 patiënten (66 ± 14 jaar oud; gemiddelde ± SD) met een ongewoon grote, de trachea vernauwende, multinodulaire struma (>100 ml), die een hoog operatierisico hadden of chirurgische behandeling weigerden. Eén dosering van 2.6 ± 1.0 GBq (70 ± 28 mCi) ^{131}I (3.7 MBq of 100 μCi per gram schildklierweefsel) werd intraveneus toegediend, gevolgd door dagelijkse toediening van L-thyroxine in doseringen die de serum TSH-spiegel niet onderdrukten. MRI metingen van het schildkliervolume, van de maximale deviatie van de trachea uit de mediaanlijn en van de kleinste dwarsdoorsnede van het lumen van de trachea werden uitgevoerd vóór en 1 jaar na de behandeling met radioactief jodium en het klinische resultaat werd beoordeeld. Kort na de ^{131}I behandeling werd geen toename van symptomen van tracheavernauwing waargenomen. Vóór de behandeling was het schildkliervolume 269 ± 153 ml en 1 jaar na de ^{131}I behandeling 154 ± 73 ml ($p < 0.001$). De reductie van het schildkliervolume was 40% ± 15% (spreiding 19% tot 60%). De maximale deviatie van de trachea (1.9 ± 0.8 cm vóór en 1.5 ± 0.7 cm 1 jaar na de behandeling) was afgenomen met 20% ± 20% (−4% tot 73%; $p < 0.001$) en de kleinste dwarsdoorsnede van het lumen van de trachea (0.78 ± 0.38 cm^2 vóór en 1.04 ± 0.48 cm^2 1 jaar na de behandeling) was toegenomen met 36% ± 38% (−3% tot 125%; $p < 0.001$). Klachten en symptomen waren verbeterd bij 8 van de 12 patiënten met kortademigheid en inspiratoire stridor en bij beide patiënten met compressie van de vena cava superior. Geconcludeerd wordt dat behandeling met radioactief jodium een effectief alternatief voor schildklierchirurgie is voor oudere patiënten met een ongewoon

grote, multinodulaire struma die compressie van de trachea en andere vitale structuren veroorzaakt.

In **hoofdstuk 8** worden dosimetrische aspecten van behandeling met radioactief jodium bij patiënten met een grote, multinodulaire struma bestudeerd. In veel van de gebruikelijke doseringsschema's voor behandeling met radioactief jodium wordt gestreefd naar een bepaalde hoeveelheid radioactief jodium per gram schildklierweefsel, 24 uur na toediening aanwezig in de schildklier. Bij toepassing van een dergelijk schema worden hoge doseringen radioactief jodium toegediend aan patiënten met een grote, multinodulaire struma. Geabsorbeerde doses in de schildklier, in omgevende weefsels en in de rest van het lichaam werden geschat na therapeutische toediening van ^{131}I (3.7 MBq per gram schildklierweefsel geretineerd in de schildklier na 24 uur) bij patiënten met een grote, multinodulaire struma (gewicht >100 gram). Thermoluminescentie dosimetrie (TLD) metingen op de huid over de schildklier, over de submandibulaire speekselklier en over de parotis werden gebruikt om de stralenbelasting voor de omgevende weefsels ten gevolge van radioactief jodium in de schildklier te benaderen. TLD-metingen bij 23 patiënten (12 eu- en 11 hyperthyreotisch; schildkliergewicht 222 ± 72 g, gemiddelde $\pm$ SD; toegediende dosis 2.1 ± 0.9 GBq) toonden cumulatieve (*i.e.* in de tijd geïntegreerde) geabsorbeerde doses van 4.2 ± 1.4 gray (Gy) op de huid over de schildklier, 2.1 ± 0.9 Gy op de huid over de submandibulaire speekselklier en 0.4 ± 0.2 Gy op de huid over de parotis. Er waren geen significante verschillen in cumulatieve doses tussen eu- en hyperthyreotische patiënten. De geabsorbeerde doses op elke van de drie locaties waren significant gecorreleerd met de totale hoeveelheid ^{131}I, geretineerd in de schildklier na 24 uur. Bij 12 patiënten (6 eu- en 6 hyperthyreotisch; schildkliergewicht 204 ± 69 g; toegediende dosis 1.9 ± 0.9 GBq) werden schattingen gemaakt van de stralenbelasting voor de schildklier en voor de rest van het lichaam. Hiervoor werd gebruik gemaakt van metingen van radioactiviteit in de schildklier en een sterk vereenvoudigd model van de jodiumkinetiek in het lichaam, zoals beschreven door Robertson en Gorman (1975). De geabsorbeerde dosis in de schildklier was 84 ± 22 Gy voor eu- en 83 ± 15 Gy voor hyperthyreotische patiënten. De hoogste geabsorbeerde doses buiten de schildklier werden berekend voor de maag, de dunne darm en de blaas (gemiddelde waarden voor 12 patiënten respectievelijk 0.38 Gy, 0.57 Gy en 0.88 Gy). De geabsorbeerde doses in alle andere weefsels en organen buiten de schildklier waren lager en variëerden van 0.05 Gy tot 0.30 Gy (gemiddelde waarden van 12 patiënten). Er waren geen significante verschillen in geabsorbeerde doses tussen eu- en hyperthyreotische patiënten. De geabsorbeerde doses in organen buiten de schildklier waren ongeveer vier maal zo hoog als die welke in de literatuur vermeld worden

voor patiënten met de ziekte van Graves na behandeling met ^{131}I. Met behulp van risicoschattingen, door het gezaghebbende International Committee on Radiation Protection voor een populatie van alle leeftijden gemaakt, werd een risico voor het ontstaan van kanker (al dan niet fataal) buiten de schildklier gedurende de rest van het leven berekend van 1.6%. Voor personen van 65 jaar en ouder is het geschatte risico lager, ongeveer 0.3%. Hierbij moet echter vermeld worden dat deze gegevens slechts risicoschattingen zijn en dat er geen werkelijke follow-up gegevens beschikbaar zijn over de kankerincidentie bij patiënten met een grote, multinodulaire struma behandeld met radioactief jodium. Bij alle patiënten met een grote, multinodulaire struma, die behandeld moeten worden wegens hyperthyreoidie of mechanische problemen, dienen de geschatte risico's van chirurgie en van behandeling met radioactief jodium tegen elkaar afgewogen te worden. Bij jongere patiënten heeft chirurgie, onzes inziens, de voorkeur, met name wanneer de toe te dienen hoeveelheid radioactief jodium, zoals berekend uit een tracer studie met ^{131}I, hoog is. Daarentegen zullen bij oudere patiënten en patiënten met cardiale of pulmonale ziekten de voordelen van niet-invasieve behandeling met ^{131}I groter zijn dan het risico ervan op lange termijn. Met name voor deze patiënten lijkt behandeling met radioactief jodium te verkiezen boven chirurgie.

Dankwoord

Graag wil ik alle mensen bedanken die meegewerkt hebben aan dit proefschrift.
Mijn beide promotores, Prof. F.H.M. Corstens en Prof. P.W.C. Kloppenborg.
Prof. J.H.J. Ruijs en Dr. J.O. Barentsz van de afdeling Radiodiagnostiek.
Prof. H. Folgering en Dr. J. Festen van het Universitair Longcentrum.
Alle patiënten die extra metingen en bloedprikken ondergingen omwille van de in dit proefschrift beschreven studies. Ik denk met veel plezier terug aan de wandelingen door het ziekenhuis met enkele van de oudere patiënten.
Alle medewerkers van de afdelingen Nucleaire Geneeskunde en Radiodiagnostiek, van het Longfunctielaboratorium en het Laboratorium Endocrinologie en Voortplanting en van de Verpleegafdeling E30 van het Radboudziekenhuis die ervoor zorgden dat de onderzoeken optimaal verliepen en dat het verblijf in het ziekenhuis voor de patiënten zo aangenaam mogelijk was.
Dit onderzoek is vooral op de "functie-kant" van de afdeling Nucleaire Geneeskunde uitgevoerd. Daarbij wil ik speciaal Wim en Marjo bedanken voor de plezierige samenwerking en vriendschap. Ook Magda, Eddie en Gerry natuurlijk bedankt. Emiel, ofschoon onze *in vitro* proefjes uiteindelijk niet beschreven zijn in het proefschrift, toch van harte bedankt voor je denkwerk en knutselarij. Ook mijn dank aan alle mensen van de afdeling Nucleaire Geneeskunde die bereid waren om in de weekeinden dosimetrie-plakkers te verwisselen.
Wil, bedankt voor je meedenken over het dosimetrie-vraagstuk. Het spijt me dat ik je zelfs tijdens het "dagje-uit" van de afdeling met mijn dosimetrie-problemen heb gestoord.
Mijn gebrek aan kennis van de statistiek en wiskunde is fantastisch gecompenseerd door mijn vader en mijn broer Marco. Ik hoop dat jullie er ook enig plezier aan beleefd hebben. Marco, daarnaast bedankt voor de verzorging van de lay-out van dit proefschrift. Pa en ma bedankt, gewoon omdat jullie er altijd zijn.
Ad, voor ons is dit proefschrift een kwestie van samen werken en samenwerken geweest. Bedankt voor het bewaken van de grote lijn van het onderzoek en voor het bekijken van de (talloze) versies van de verschillende artikelen.
Ten slotte mijn dank aan Stoffer voor het kritisch doorlezen van het dosimetrie-artikel en aan de "Weezenlanders" en alle anderen die hun belangstelling toonden voor mijn onderzoeksperikelen.

Curriculum vitæ

Dyde Huysmans werd op 26 april 1963 geboren in Breda. Van 1975 tot 1981 bezocht zij het College van het Heilig Kruis te Uden. Tijdens de laatste twee jaren van deze periode werd de vooropleiding voor het conservatorium gevolgd (hoofdvakken harp en piano). In 1981 begon zij aan de studie geneeskunde aan de Katholieke Universiteit te Nijmegen. In 1986 werd het doctoraalexamen behaald en in 1988 het artsexamen. Van mei 1988 tot september 1989 was zij werkzaam als arts-assistent interne geneeskunde in het St. Josephziekenhuis te Eindhoven (Opleider: Dr. P. Gerlag), waarvan het laatste jaar in het kader van de opleiding tot nucleair geneeskundige. Deze opleiding werd vanaf september 1989 voortgezet op de afdeling Nucleaire Geneeskunde van het Academisch Ziekenhuis Nijmegen (Hoofd: Prof. Dr. F.H.M. Corstens). Tijdens de opleiding werd het diploma Stralingsdeskundige niveau C behaald. In september 1992 vond de registratie tot nucleair geneeskundige plaats. Tot mei 1994 was zij werkzaam op de afdeling Nucleaire Geneeskunde van het Academisch Ziekenhuis Nijmegen en verrichtte zij tevens de beoordeling van radiopharmaca ten behoeve van het College ter Beoordeling van Geneesmiddelen. Sinds mei 1994 is zij als nucleair geneeskundige werkzaam in ziekenhuis De Weezenlanden te Zwolle. Zij is gehuwd met Ad Hermus.